

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMNEAL PHARMACEUTICALS, INC. AND KASHIV BIOSCIENCES,
Petitioner,

v.

GENENTECH, INC.,
Patent Owner.

Case No. IPR2026-00260
Patent No. 12,030,959

**DECLARATION OF DR. ASIF RAFI
IN SUPPORT OF PETITION FOR INTER PARTES REVIEW OF
U.S. PATENT NO. 12,030,959**

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I, Asif Rafi, MD, declare as follows:

I. INTRODUCTION

1. I have been retained by counsel for Amneal as a technical expert in connection with the above-identified proceeding. I have been asked to provide my opinions concerning the “novelty” and “obviousness” of claims 1-29 of U.S. Patent No. 12,030,959 (“*US959*”) (EX1001), which relate to “method[s] of treating a human subject having an allergy to a food allergen” by administering omalizumab, wherein the dosage amount/frequency vary depending on the subject’s weight (10-15 kg) and baseline total serum IgE (Immunoglobulin E) (30-1850 IU/mL). I understand that my declaration will be submitted in support of Amneal’s Petition for Inter Partes Review of *US959* against Genentech, Inc. (“Genentech” or “Patent Owner”).

2. My opinions in this declaration are based on my review of *US959* (EX1001), portions of its prosecution history (EX1004), the relevant prior art that I have identified and of which I have been informed, other documents referred to in this declaration, the documents listed in Appendix 1, and my many years of experience in the industry with the treatment of food allergies and other allergic ailments, such as allergic asthma, including during the relevant time period for the questions I have been asked to consider.

3. I am being compensated for my time at my usual consulting rate of \$700 per hour. I am also being reimbursed for reasonable travel expenses related to my consultation. I do not have a personal or financial interest in the outcome of this proceeding, and my compensation is not affected by its outcome.

II. BACKGROUND AND QUALIFICATIONS

4. I am currently the CEO of Asif Rafi, MD Inc., an academic private practice with more than 6500 adult and pediatric patients with allergic and immunologic diseases. I subspecialize in, among other things, the treatment of food allergy, chronic rhinosinusitis (CRS), humoral immune deficiencies, asthma, eosinophilic disorders, allergic bowel disease, and allergic skin disorders. I have extensive experience in treating patients with allergic disorders, including the treatment of infants, adolescents, young adults and adults. I also have extensive experience treating those patients with omalizumab and other medications for the treatment of allergic and immunologic diseases.

5. I have a Bachelor of Science in Biology from the University of Maryland and a Doctor of Medicine (MD) from Howard University College of Medicine.

6. After earning my MD in 1998, I was an internal medicine resident at Johns Hopkins University Medical Center/Sinai from 1998-2001. I then completed a geriatric medicine fellowship at UCLA from 2002-2003, a special fellowship in

advanced geriatrics and immunology at UCLA/VA Medical Center, Division of Geriatrics and Gerontology from 2003-2005, and an allergy and immunology fellowship at VA medical Center/UCLA from 2002-2005.

7. After completing my residency and fellowships, I became a Clinical Instructor at the VA Greater Los Angeles Healthcare System/UCLA School of Medicine. Thereafter, I became an Assistant Clinical Professor and then an Associate Clinical Professor of Medicine. I also was a core faculty member and taught at the Allergy and Immunology Fellowship Program, where I was actively involved in clinical research.

8. From 2005-2014, I was a full-time academic private practice physician at the Asthma and Allergy Care Center in Los Angeles, California, where my patients included an equal mix of adults and pediatric patients. While at the Asthma and Allergy Care Center, I conducted significant research including three active clinical trials. This research included a prospective and retrospective analysis of the pathophysiology and treatment outcomes of allergic diseases in more than 200 omalizumab patients, as well as the PROSPERO clinical trial.

9. I have extensive experience related to the diagnosis and treatment of atopic dermatitis, food allergy, CSU, eosinophilic esophagitis, chronic rhinosinusitis, and eosinophilic bowel disease, including the use of omalizumab to treat these conditions.

10. I have extensive experience treating pediatric patients. I first treated such patients in 2000-2002 while working as a staff physician at Patient First in Baltimore, Maryland. Thereafter, I treated patients during my Allergy fellowship in 2002, my pediatric training at the Children's Hospital of Los Angeles ("CHLA") between 2002-2005, and in private practice beginning in 2005 and continuing to the present day. My practice currently has a large pediatric population.

11. I have authored or co-authored a number of peer-reviewed articles, abstracts, and presentations, including those concerning the study of food allergy. For example, I authored Asif Rafi et al., *Effects of omalizumab in patients with food allergy*, 31 ALLERGY AND ASTHMA PROC. 76 (2010) ("*Rafi*") (EX1023), one of the earliest articles regarding the use of omalizumab for the treatment of food allergy.

III. LEGAL STANDARDS

12. I do not hold any legal qualifications; however, Amneal's counsel has informed me of a number of legal principles to consider when formulating my opinions relating to the validity of *US959*. These principles are set forth below.

A. Claim Construction

13. I understand that in an IPR proceeding, the terms in a patent claim are generally given their ordinary and customary meaning as understood by a person of ordinary skill in the art ("POSA") in the context of the entire patent disclosure.

If, however, an inventor defines a claim term in the patent disclosure, then the inventor's definition applies. But if the inventor chooses to define a claim term, the inventor must do so with reasonable clarity, deliberateness, and precision.

14. I further understand that claims can be "independent" or "dependent." An independent claim does not refer to or incorporate the elements of any other claim. A dependent claim refers to another claim and includes all its limitations while also adding one or more additional limitations. Claims 1-29 of *US959* include four independent claims: claims 1, 12, 17, and 25. Claims 2-11 depend directly or indirectly from claim 1; claims 13-16 depend from claim 12; claims 18-24 depend directly or indirectly from claim 17; and claim 26-29 depend from claim 25.

15. I understand that the common use of the word "or" is as a designator of alternatives.

B. Burden of Proof

16. I understand that in an IPR, a claim is not patentable if a "preponderance of the evidence" establishes that the claim is anticipated by, or rendered obvious by, the prior art. I understand that "a preponderance of the evidence" means "more likely than not."

C. Prior Art and Earliest Effective Filing Date

17. I understand that in order to obtain the benefit of an earlier filed application, including a provisional application, the later-filed application must claim an invention that is also disclosed in the prior application and the disclosure of the invention in the prior and later filed applications must satisfy enablement and written description.

18. As I discuss below in Paragraphs 51 and 158, I have been informed that the earliest possible effective filing date for *US959* is July 5, 2023. I have thus been asked to assume that any printed publication published prior to that date should be considered “prior art” to the patent.

19. I further understand that a document is considered a “printed publication” if it was published or otherwise made available such that a POSA exercising reasonable diligence could have located it.

D. Anticipation

20. I have been informed and understand that for a patent claim to be patentable, it must be novel.

21. I have been informed and understand that a patent claim is “anticipated” if a single prior art reference discloses to a POSA every element of the claim arranged as in the claim.

22. I have been informed that a member of a genus, that is, a species, anticipates a genus.

23. I have been informed that if a claim uses the word “or” to present alternative limitations, if any of the alternatives in a claim are anticipated by the prior art, then the claim is invalid. Put another way, I have been informed that even if only one such alternative in a claim is anticipated by the prior art, then the claim is invalid.

24. I have also been informed that if a claim describes a functional result, it is considered the natural result flowing from the prior art if the patent teaches that the only steps required to achieve the functional result are the same as those disclosed in the prior art. In other words, when the patent does not itself disclose any more than what is in the prior art regarding how to achieve a claimed functional result, then the functional result is considered the natural result of those steps.

25. I understand that a prior art publication must be “enabling” in order to anticipate a patent claim. Prior art is enabling if it describes the claimed invention sufficiently to allow a POSA to carry out the invention.

26. I have been informed and understand that, in an anticipation analysis, there is no need to consider secondary considerations.

E. Obviousness

27. I understand from counsel that for a patent claim to be patentable, it must be “non-obvious” over the prior art.

28. I understand that a patent claim is obvious if the differences between the claims and the prior art are such that the subject matter as a whole would have been obvious to a POSA at the time the invention was made.

29. I understand that when assessing whether a claim is obvious, I should consider: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the prior art and what is claimed; and (4) any “secondary” evidence that may indicate that the claims are not obvious.

30. I understand that a claimed invention may be obvious when, for example, there is some motivation, reason, or suggestion that would have led a POSA to modify a prior-art reference or to combine prior-art teachings to arrive at the claimed invention.

31. I also understand that when combining or modifying prior-art references to arrive at the claimed invention, the POSA must also have a reasonable expectation of success, given their general knowledge and what has been disclosed in the prior art. I understand that this success need only be reasonably expected and does not need to be guaranteed or proven.

32. I understand further that if a member of a genus, that is, a species, is obvious, then the genus is also obvious.

33. I have been informed that if a claim uses the word “or” to present alternative limitations, if any of the alternatives in a claim are rendered obvious by the prior art, then the claim is invalid. Put another way, I have been informed that even if only one such alternative in a claim is rendered obvious by the prior art, then the claim is invalid.

34. I have been informed that “secondary” evidence may weigh against a finding that a claimed invention would have been obvious. Such secondary evidence may include: (1) commercial success of a product due to the merits of the features of the product that are the subject of the patent claims; (2) a long-felt but unresolved need for the solution provided by the patent claim; (3) unsuccessful attempts by others to find the solution provided; and (4) unexpected results. I have also been informed that “secondary” evidence is also referred to as objective indicia of non-obviousness.

35. In forming my opinions regarding what would have been obvious to a POSA at the relevant time, I have not relied on hindsight, nor have I used any confidential, proprietary, or uniquely personal knowledge that would not have been available to a POSA.

F. The POSA

36. I understand that claim construction, anticipation, and obviousness must be judged from the perspective of the POSA to which the patent is directed. I understand that the POSA is a hypothetical person or persons that is/are presumed to have perfect knowledge of all the relevant prior art.

37. I understand that in determining who a POSA is the following may be considered: (1) the educational level of the inventor(s); (2) the type of problems encountered in the relevant technical field; (3) prior-art solutions to those problems; (4) rapidity with which innovations are made; and (5) the sophistication of the technology and educational level of active workers in the field.

38. *US959* concerns administering omalizumab to treat food allergies in subjects weighing 10 to 15 kg, wherein the omalizumab dose is based on the subject's weight and pre-treatment total serum IgE. Based on my extensive experience using omalizumab to treat subjects with IgE mediated allergies, the POSA at the time of the invention would have been a medical doctor and/or clinical researcher with a Ph.D. and significant experience treating and/or researching food and other allergies. The POSA would have collaborated with others, including scientists skilled in related fields typically employed in pharmaceutical development, such as pharmacokineticists and formulators.

IV. OVERVIEW OF *US959* AND ITS PROSECUTION HISTORY

A. Overview of *US959*

39. *US959* is titled “ANTI-IgE Antibody Therapy for Multiple Food Allergies.” EX1001. Based on information on the face of the patent, *US959* is assigned to Genentech, Inc. *Id.*

40. I have reviewed the claims, specification, and portions of the prosecution history of *US959*.

41. *US959* describes the invention as methods for “treating a subject having or diagnosed with a food allergy to one or more food allergens” by administering “an anti-IgE antibody at a specific dose and frequency to a human subject who is allergic to one or more food allergens.” EX1001, 1:66-2:5.

42. *US959* explains that “[f]ood allergies affect approximately 15 million patients in the U.S., including six million children” (*id.*, 1:40-41) and are “the most common cause of anaphylaxis in pediatric patients seen in emergency departments across the U.S,” causing both morbidity and mortality (*id.*, 1:42-44).

43. *US959* notes that while an oral immunotherapy (OIT) has been approved in the U.S. for peanut allergy, 40% to 70% of children with peanut allergies are also allergic to other foods, creating a need for treatments for patients with multiple food allergies. *Id.*, 1:53-62.

44. *US959* notes that in Stage 1 of a Phase 3 clinical study of the use of omalizumab to patients subjects with a food allergy (the OUtMATCH study), and states that in stage 1 of the study omalizumab was found to be “surprisingly safe and effective” for young children, 1-5 years of age, an age range for which previous omalizumab indications had not been approved. *Id.*, 2:43-54. According to *US959*, this was a major advance in the treatment of children with food allergies, and required design of a new dosing table for patients with body weights of 10-20 kg and baseline total serum IgE levels as high as 1850 IU/mL. *Id.*, 2:54-65.

45. *US959* states that “it was important to determine doses which were high enough to produce a therapeutic benefit by reducing levels of serum IgE from relatively high baseline levels while also ensuring an acceptable safety profile. *Id.*, 3:10-13.

46. Example 1 of the *US959* describes the OUtMATCH Phase 3 clinical trial testing the use of omalizumab for treating patients that are allergic to one or more foods. *Id.*, col. 32-col. 44, Example 1. The study was open to patients aged 1 to 55 with allergies to peanuts and two other foods, such as milk, egg, wheat, cashew, hazelnut, and walnut. *Id.*, 32:50-53.

47. *US959* states that in the OUtMATCH clinical trial, omalizumab was dosed according to the dosing table of Figure 2, reproduced below:

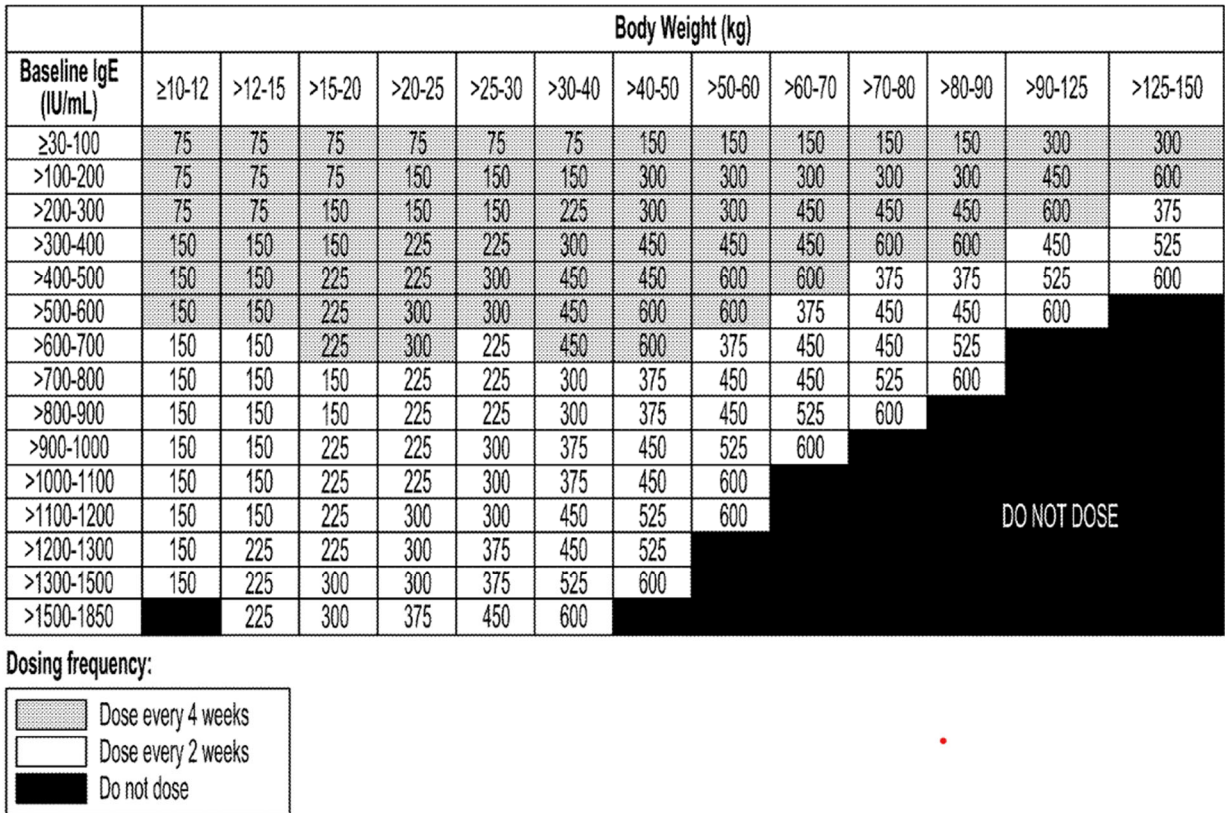


FIG. 2

Id., FIG 2; 33:32-34.

48. *US959* explains that the first 60 subjects to complete Stage 1 were selected for an Open Label Extension (OLE), in which the subjects received open label omalizumab during weeks 24-28, after which each subject completed a double-blinded, placebo-controlled, food challenge (“DBPCFC”) “consisting of placebo and each of their three specific foods to a cumulative dose of 8044 mg protein of each food.” *Id.*, 33:40-46. According to *US959*:

The study met the primary endpoint and achieved statistical significance on the proportion of participants who could consume a single dose of >600 mg of peanut protein without dose-limiting symptoms during the DBPCFC at the end of

Stage 1. In the omalizumab-treated group, 68.2% of participants passed the DBPCFC compared to 5.5% in placebo (A: 62.7%, OR: 37.14, $p < 0.00001$).

Id., 40:1-7.

49. *US959* has 29 claims. Claims 1, 12, 17, and 25 are independent.

Claims 2-11 depend directly or indirectly from claim 1, claims 13-16 depend from claim 12, claims 18-24 depend directly or indirectly from claim 17, and claims 26-29 depend from claim 25. All claims are reproduced below.

1. A method of treating a human subject having an allergy to a food allergen, the method comprising:
administering to the subject by subcutaneous injection a pharmaceutical composition comprising a dose of omalizumab,
wherein the pharmaceutical composition is administered once about every two weeks and the dose of omalizumab is from 150 mg to 225 mg, or the pharmaceutical composition is administered once about every four weeks and the dose of omalizumab is from 75 mg to 150 mg, and
wherein body weight of the subject is equal to or greater than 10 kg and less than or equal to 15 kg, and total serum IgE level of the subject is equal to or greater than 30 IU/ml and less than or equal to 1850 IU/ml.
2. The method of claim 1, wherein the pharmaceutical composition is administered once about every two weeks and the dose of omalizumab is:
150 mg when the body weight of the subject is equal to or greater than 10 kg and less than or equal to 12 kg, and the total serum IgE level of the subject is greater than 600 IU/ml and less than or equal to 1500 IU/ml;
or
150 mg when the body weight of the subject is greater than 12 kg and less than or equal to 15 kg, and the total serum IgE level of the subject is greater than 600 IU/ml and less than or equal to 1200 IU/ml; or
225 mg when the body weight of the subject is greater than 12 kg and less than or equal to 15 kg, and the total serum IgE level of the subject is greater than 1200 IU/ml and less than or equal to 1850 IU/ml; and
wherein the total serum IgE level of the subject is determined prior to administration of a first dose of omalizumab.
3. The method of claim 1, wherein the pharmaceutical composition is administered once about every four weeks and the dose of omalizumab is:
75 mg when the body weight of the subject is equal to or greater than 10 kg and less than or equal to 15 kg, and the total serum IgE level of the subject is equal to or greater than 30 IU/ml and less than or equal to 300 IU/ml; and
wherein the total serum IgE level of the subject is determined prior to administration of a first dose of omalizumab.
4. The method of claim 1, wherein the pharmaceutical composition is administered once about every four weeks and the dose of omalizumab is:

150 mg when the body weight of the subject is equal to or greater than 10 kg and less than or equal to 15 kg, and the total serum IgE level of the subject is greater than 300 IU/ml and less than or equal to 600 IU/ml; and

wherein the total serum IgE level of the subject is determined prior to administration of a first dose of omalizumab.

5. The method of claim 1, wherein the pharmaceutical composition is administered to a subject having a body weight of greater than 12 kg and less than or equal to 15 kg at a dose of:

75 mg once about every four weeks if the total serum IgE level of the subject is equal to or greater than 30 IU/ml and less than or equal to 300 IU/ml; or

150 mg once about every four weeks if the total serum IgE level of the subject is greater than 300 IU/ml and less than or equal to 600 IU/ml; or

150 mg once about every two weeks if the total serum IgE level of the subject is greater than 600 IU/ml and less than or equal to 1200 IU/ml; or

225 mg once about every two weeks if the total serum IgE level of the subject is greater than 1200 IU/ml and less than or equal to 1850 IU/ml; and

wherein the total serum IgE level of the subject is determined prior to administration of a first dose of omalizumab.

6. The method of claim 2, wherein the body weight of the subject is determined prior to administration of a first dose of omalizumab.

7. The method of claim 2, wherein the subject is not receiving concurrent oral immunotherapy with the food allergen.

8. The method of claim 2, wherein treating comprises reducing an allergic reaction following accidental exposure of the subject to the food allergen.

9. The method of claim 2, wherein treating comprises reducing a moderate-to-severe allergic reaction following exposure of the subject to the food allergen.

10. The method of claim 1, wherein the pharmaceutical composition is administered once about every two weeks and the dose of omalizumab is:

150 mg when the body weight of the subject is equal to or greater than 10 kg and less than or equal to 15 kg, and the total serum IgE level of the subject is greater than 600 IU/ml and less than or equal to 1200 IU/ml; or

150 mg when the body weight of the subject is equal to or greater than 10 kg and less than or equal to 12 kg,

and the total serum IgE level of the subject is greater than 1200 IU/ml and less than or equal to 1500 IU/ml; and

wherein the total serum IgE level of the subject is determined prior to administration of a first dose of omalizumab.

11. The method of claim 1, wherein the pharmaceutical composition is administered once about every four weeks and the dose of omalizumab is:

75 mg when the body weight of the subject is equal to or greater than 10 kg and less than or equal to 15 kg, and the total serum IgE level of the subject is equal to or greater than 30 IU/ml and less than or equal to 300 IU/ml; or

150 mg when the body weight of the subject is equal to or greater than 10 kg and less than or equal to 15 kg, and the total serum IgE level of the subject is greater than 300 IU/ml and less than or equal to 600 IU/ml; and wherein the total serum IgE level of the subject is determined prior to administration of a first dose of omalizumab.

12. A method of treating a human subject having an allergy to a food allergen, the method comprising:

(i) administering to the subject by subcutaneous injection once about every four weeks a pharmaceutical composition comprising a dose of omalizumab of:

150 mg when body weight of the subject is equal to or greater than 10 kg and less than or equal to 15 kg, and total serum IgE level of the subject is greater than 300 IU/ml and less than or equal to 600 IU/ml; or

(ii) administering to the subject by subcutaneous injection once about every two weeks a pharmaceutical composition comprising a dose of omalizumab of:

150 mg when body weight of the subject is equal to or greater than 10 kg and less than or equal to 12 kg, and total serum IgE level of the subject is greater than 600 IU/ml and less than or equal to 1500 IU/ml; or

150 mg when body weight of the subject is greater than 12 kg and less than or equal to 15 kg, and total serum IgE level of the subject is greater than 600 IU/ml and less than or equal to 1200 IU/ml; or

225 mg when body weight of the subject is greater than 12 kg and less than or equal to 15 kg, and total serum IgE level of the subject is greater than 1200 IU/ml and less than or equal to 1850 IU/ml; and

wherein the total serum IgE level of the subject is determined prior to administration of a first dose of omalizumab.

13. The method of claim 12, wherein the body weight of the subject is determined prior to administration of a first dose of omalizumab.

14. The method of claim 12, wherein treating comprises reducing a moderate-to-severe allergic reaction following exposure of the subject to the food allergen.

15. The method of claim 12, wherein treating comprises reducing an allergic reaction following accidental exposure of the subject to the food allergen.

16. The method of claim 12, wherein the subject is not receiving concurrent oral immunotherapy with the food allergen.

17. A method of treating a human subject having an allergy to a food allergen, the method comprising:

(i) administering to the subject by subcutaneous injection once about every four weeks a pharmaceutical composition comprising a dose of omalizumab of:

75 mg when body weight of the subject is equal to or greater than 10 kg and less than or equal to 15 kg, and

total serum IgE level of the subject is equal to or greater than 30 IU/ml and less than or equal to 300 IU/ml; or 150 mg when body weight of the subject is equal to or greater than 10 kg and less than or equal to 15 kg, and total serum IgE level of the subject is greater than 300 IU/ml and less than or equal to 600 IU/ml; or

(ii) administering to the subject by subcutaneous injection once about every two weeks a pharmaceutical composition comprising a dose of omalizumab of:

150 mg when body weight of the subject is equal to or greater than 10 kg and less than or equal to 12 kg, and total serum IgE level of the subject is greater than 600 IU/ml and less than or equal to 1500 IU/ml; or

150 mg when body weight of the subject is greater than 12 kg and less than or equal to 15 kg, and total serum IgE level of the subject is greater than 600 IU/ml and less than or equal to 1200 IU/ml; or

225 mg when body weight of the subject is greater than 12 kg and less than or equal to 15 kg, and total serum IgE level of the subject is greater than 1200 IU/ml and less than or equal to 1850 IU/ml; and

wherein the total serum IgE level of the subject is determined prior to administration of a first dose of omalizumab.

18. The method of claim 17, wherein the body weight of the subject is determined prior to administration of a first dose of omalizumab.

19. The method of claim 17, wherein the subject is not receiving concurrent oral immunotherapy with the food allergen.

20. The method of claim 17, wherein the subject is from 1 year to 5 years of age.

21. The method of claim 17, wherein the subject has an allergy to peanut and to one or more of milk, egg, and cashew.

22. The method of claim 17, wherein treating comprises reducing an allergic reaction following exposure of the subject to the food allergen.

23. The method of claim 22, wherein the exposure to the food allergen is accidental.

24. The method of claim 22, wherein the allergic reaction is a moderate-to-severe allergic reaction.

25. A method of treating a human subject having an allergy to a food allergen, the method comprising:

administering to the subject having a body weight equal to or greater than 10 kg and less than or equal to 12 kg by subcutaneous injection a pharmaceutical composition comprising a dose of omalizumab of:

75 mg once about every four weeks if total serum IgE level of the subject is equal to or greater than 30 IU/ml and less than or equal to 300 IU/ml; or

150 mg once about every four weeks if total serum IgE level of the subject is greater than 300 IU/ml and less than or equal to 600 IU/ml; or

150 mg once about every two weeks if total serum IgE level of the subject is greater than 600 IU/ml and less than or equal to 1500 IU/ml; and

wherein the total serum IgE level of the subject is determined prior to administration of a first dose of omalizumab.

26. The method of claim 25, wherein the body weight of the subject is determined prior to administration of a first dose of omalizumab.

27. The method of claim 25, wherein treating comprises reducing a moderate-to-severe allergic reaction following exposure of the subject to the food allergen.

28. The method of claim 25, wherein treating comprises reducing an allergic reaction following accidental exposure of the subject to the food allergen.

29. The method of claim 25, wherein the subject is not receiving concurrent oral immunotherapy with the food allergen.

B. Prosecution History

50. *US959* issued on July 9, 2024. It lists Ryan Patrick Owen, Ahmar Iqbal, and Robert A. Wood as inventors and states that it is assigned to Genentech, Inc. EX1001, 1.

51. I have been informed that the underlying application that issued as *US959* is Application No. 18/486,053 (“*App053*”). *US959* states that *App053* was filed on October 12, 2023 and is a continuation of application No. PCT/US2023/070639, filed on July 20, 2023. I have been informed that *US959* claims the benefit of provisional application 63/512,051 filed on July 5, 2023. EX1001, 1.

52. I have reviewed portions of the prosecution history of *US959*. I discuss some of these portions below in the context of my analysis related to my opinion that claims 1-29 of *US959* are not patentable because they are anticipated and/or obvious. For example, the May 22, 2024, Notice of Allowability states:

Applicant has claimed methods of treating food allergies by administering omalizumab. Administering omalizumab to treat food allergies, such as peanut allergies, was known in the prior art. See for example U.S. Patent No. 10,034,940. However, the

instant claims recite a relationship between the mass of omalizumab administered to the patient, the body mass of the patient, the disease severity as measured by total serum IgE, and the time interval between administrations that was not disclosed in the prior art, nor do the instant recited limitations appear to be obvious variations of prior art dosing protocols. Indeed, the instant recited patient masses are smaller than those found in dosing charts such as those of the FDA prescribing label for XOLAIR (aka omalizumab, see reference 43 on the 4/30/24 IDS) and thus data on the pediatric patients encompassed by the claimed methods (which even though not recited as being “pediatric,” humans of the recited body masses realistically can only be young children) was not present in the prior art. Note that the instant claimed methods provide clinical benefits to children within the recited body mass ranges as demonstrated by the clinical data disclosed in the instant specification. See Example 1, most particularly pages 55-59 and Tables 1.4 and 1.5). Artisans would reasonably have no trouble whatsoever following the instant recited dosing protocol, and administration of antibodies, including omalizumab, is quite routine in the medical arts as again evidenced by the '940 patent. Therefore the instant claimed inventions have been found to be allowable.

EX1004, 175-176.

53. As explained below, in my opinion the prior art expressly discloses all of the limitations of many of the claims. Those claims, as I explain below, are “anticipated” by the prior art. As I also explain below, the treatment method of all of the claims would have been obvious to a person of ordinary skill in the art in view of the prior art, including the dosing of pediatric patients with omalizumab as encompassed by the claims (*see, e.g.*, Paragraphs 219-231) and the relationship between the mass of omalizumab administered to the patient, the body mass of the

patient, the disease severity as measured by total serum IgE, and the time interval between administrations (*see, e.g.*, Paragraphs 232-244).

V. SCIENTIFIC BACKGROUND

A. Food Allergy

54. As explained below in Paragraphs 55 and 219, as of July 2022, a POSA would have known that food allergy impacts millions of children and has been increasing. Food allergy is the main etiology of anaphylaxis among children, significantly impacts quality of life for children and their families, and has a high economic cost. For these reasons and those state below, a POSA would have been motivated to find new safe and effective treatments for food allergy in children.

55. As of July 2022, a POSA would have known that the prevalence of food allergy had been increasing, particularly in children (EX1035, 1), with one study estimating that the prevalence of food allergy in children had increased 1-2% per decade (EX1041, 65). It was estimated that close to six million children in the U.S. had food allergies (*id.*) and surveys had estimated that more than 40% of children with food allergies had experienced a severe allergic reaction requiring an emergency room visit (*id.*, citing EX1042). Other studies had estimated that as of 2018, food allergies affected more than 4.8 million children a year and were the main cause of anaphylaxis among children. EX1021, 1; EX1006, 286. For example, the *OUtMATCH* study, discussed below, likewise stated that “[f]ood

allergy affects about 15 million people in the United States,” that “[t]his includes 6 million children,” that “[t]he current treatment for food allergy is to avoid eating the foods that may cause an allergic reaction and have medications such as epinephrine (adrenaline) in case of a reaction,” and that “[t]he risks of accidental exposures and life-threatening reactions can place a large burden on patients and their families.” EX1005, 5.

56. A POSA would have known that “[u]p to 8% of the pediatric population suffers from food allergy and of those 30% have clinical reactivity to more than one food allergen.” EX1009, 1; *see also* EX1011, 1. “Compared to those with single food allergies, multi-sensitized subjects experience a greater decrease in quality of life, are more likely to suffer from dietary deficiencies and are less prone to spontaneously outgrow their allergies.” EX1009, 1.

57. Children with multifood allergies faced constant risk of accidentally ingesting a food to which they are allergic, with the concomitant risk of a severe allergic reactions, such as near-fatal, or fatal, anaphylaxis. EX1018, 16; EX1022, 2. Genentech’s 2018 press release regarding XOLAIR receiving breakthrough therapy designation for the treatment of food allergies stated that food allergies were estimated to be responsible for about 200,000 emergency room visits a year. EX1011, 1.

58. Food allergies therefore placed heavy burdens on children and their families, causing time lost from work, emergency room visits, and career changes, with economic costs of billions of dollars a year. EX1009, 1.

59. A POSA thus would have understood that reducing the risk of severe allergic reactions would reduce the allergy-associated stress in patients and families. EX1018, 22.

60. As explained below, long before the filing of *US959* there was extensive data in the literature regarding the high incidence of severe food allergy in pediatric patients, including in patients in the 10-15 kg weight range. The management of these patients (young children with severe food allergy) was thus front and center in the literature long before the filing of *US959*.

61. IgE was known to play a role in food allergies. “The incidence of IgE-mediated forms [of food allergies], typically rapid in onset, range from 1% to 10% in infants and preschool-aged children, from 1% to 5% in school age, and about 4.5% in adults. Most ... are mild or moderate, but some become severe and potentially life-threatening, culminating in IgE-mediated anaphylaxis.” EX1030, 1007.

62. Treatments evaluated by those in the field included food avoidance, which was generally not preferred as it did nothing to address the underlying allergy. Another option that had been extensively evaluated was oral

immunotherapy (OIT). Oral Immunotherapy (OIT) works by inducing desensitization—a higher threshold for allergic reactions—through daily, controlled consumption of increasing amounts of an allergen. This process modulates the immune system by raising allergen-specific IgG4 (blocking antibodies), reducing specific IgE, decreasing T-helper 2 (Th2) activity, and promoting Treg cell responses. The drawback of this treatment is that suspension of OIT often leads to the reappearance of symptoms. *See* EX1030, 1008.

63. Pharmaceutical treatments, alone or in combination with OIT, have been extensively investigated. It was reported in the literature that IgE “is an obvious target for biological therapy, and the one most widely studied.” EX1030, 1011. As discussed below, omalizumab in particular was known to be safe and efficacious for treating food allergy. Those in the field expected that omalizumab would be safe and effective for the treatment of food allergy in young children, and they would have been surprised only if the data indicated otherwise. Paragraphs 118-122.

B. Omalizumab For the Treatment of IgE-Mediated Allergic Reactions

64. Genentech’s trade name for omalizumab is XOLAIR. *See* EX1007, 1. By 2021, XOLAIR was approved for the treatment of moderate-to-severe persistent allergic asthma in patients as young as six years of age, chronic rhinosinusitis with nasal polyps (CRSwNP), and chronic spontaneous urticaria

(CSU). *See* EX1007, 1. By then, it had already been on the market for nearly two decades. *See* EX1050, 17. As explained in the July 2021 prescribing information for XOLAIR (*PI2021*), “[o]malizumab inhibits the binding of IgE [Immunoglobulin E] to the high-affinity IgE receptor (FcεRI) on the surface of mast cells, basophils, and dendritic cells, resulting in FcεRI down-regulation on these cells. In allergic asthmatics, treatment with omalizumab inhibits IgE-mediated inflammation, as evidenced by reduced blood and tissue eosinophils and reduced inflammatory mediators, including IL-4, IL-5, and IL-13.” EX1007, 22.

65. Specifically, omalizumab was known to bind the constant region of IgE, allowing it to reduce circulating IgE antibodies and inducing a generalized dampening of type 1 allergic immunity. EX1006, 287; EX1028, 72. IgE is then prevented from attaching to mast cells and basophils, and FcεRI receptor expression is down-regulated. EX1046, Abstract. This made omalizumab an attractive candidate for treatment of IgE mediated diseases. EX1006, 287; EX1028, 72. As discussed below, such IgE mediated diseases were known to include, *e.g.*, allergic asthma and Ige-mediated food allergy. EX1006, 287.

66. The known mode of action of omalizumab was demonstrated in the Figure below, reproduced from Figure 1 of *Kopp*.

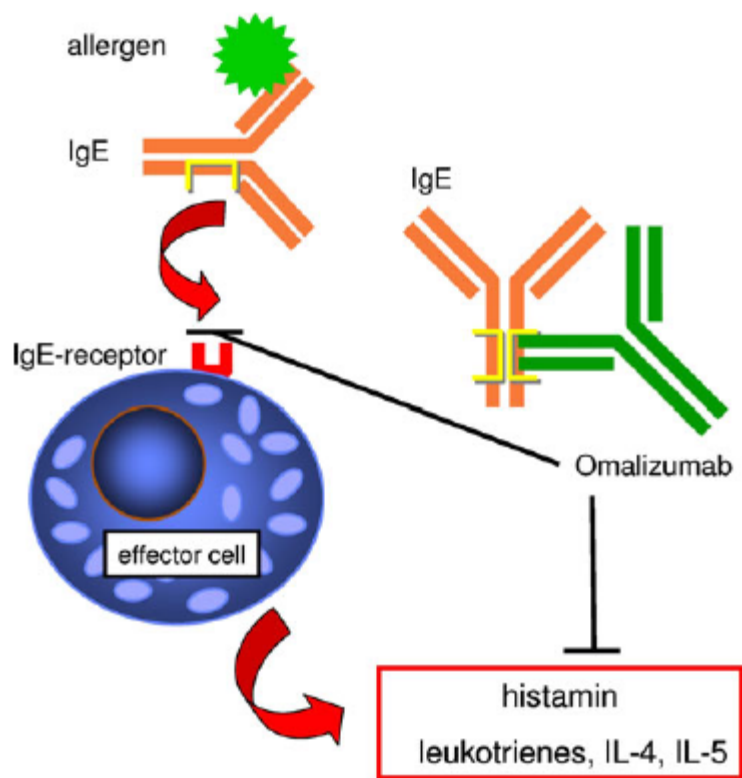


Fig. 1 Mode of action of omalizumab. Omalizumab decreases the levels of circulating IgE regardless of allergen specificity by binding to the constant region of the circulating IgE molecule, which prevents free IgE from interacting with the high- and low-affinity IgE receptors (FcεRI and FcεRII) on effector cells. IL—interleukin

EX1038, 102, Fig. 1. As shown in the above figure, omalizumab binds to the constant region and thereby reduces the level of circulating free IgE, regardless of allergen specificity. This prevents IgE from interacting with IgE receptors on effector cells, which prevents the release of histamine and leukotrienes, IL-4 and IL-5, which are involved in allergic reactions. EX1038, 102, Fig. 1.

67. *Arasi* likewise describes omalizumab's mechanism of action.

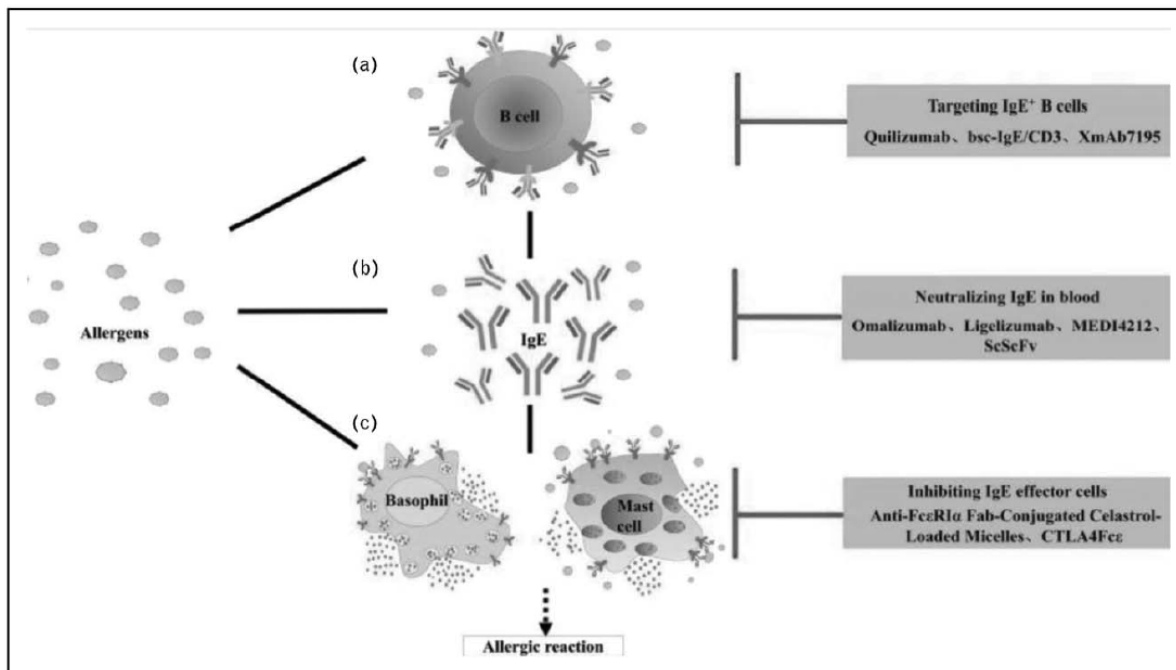


FIGURE 1. Different options for anti-IgE strategy: a. Inhibition of IgE + B cells (Quilizumab). b. Serum IgE neutralization (Immuno adsorption plasma-pheresis, Omalizumab, Ligelizumab, their biosimilars CMAB007 and MEDI4212, and recombinant ScFv (a single-chain antibody targeting IgE, IgE-bound cells, and IgE-secreting cells). c. Inhibition of IgE-effector cells (Anti-FcεRI Fab-conjugated celastrol-loaded micelles aimed to prevent IgE interaction with mast cells, and kill mast cells, CTLA4FcεFusion protein targeting IgE receptors, FcεRI and FcεRII/CD23. Reproduced from Hu *et al.* [9].

EX1006, 286-287.

68. By selectively binding to the constant region of IgE, omalizumab reduces blood levels of free IgE. EX1022, 2; EX1007, 22. As described in *PI2021*, during clinical trials, serum free IgE was reduced by more than 96% when using recommended doses: “In clinical studies, serum free IgE levels were reduced in a dose-dependent manner within 1 hour following the first dose and maintained between doses. Mean serum free IgE decrease was greater than 96% using recommended doses.” EX1007, 22.

69. While administration of omalizumab reduces serum free (unbound) IgE levels in a dose-dependent manner, it was known that omalizumab actually

increases total serum IgE (bound and unbound) because of the formation of omalizumab-IgE complexes that are eliminated from the body more slowly than free IgE: “Serum total IgE levels (i.e., bound and unbound) increased after the first dose due to the formation of omalizumab:IgE complexes, which have a slower elimination rate compared with free IgE.” EX1007, 22. Accordingly, a POSA would have known the importance of measuring serum total IgE before the first dose of omalizumab.

70. As explained in *Crisafulli*, the clinical efficacy and safety of omalizumab had been extensively demonstrated in many studies, including in pediatric patients. EX1043, 1; *see also* EX1046, 56-57.

71. *Crisafulli* further explained that several clinical trials saw promising results when using omalizumab to treat a wide range of diseases in which IgE plays a role: “Several clinical trials have also explored the use of the Omalizumab in the treatment of other diseases in which IgE play a role (such as allergic rhinitis, food and drugs allergy, anaphylaxis, keratoconjunctivitis, urticaria, angioedema, allergic bronchopulmonary aspergillosis, atopic dermatitis, non-allergic asthma, Churg-Strauss syndrome, nasal polyposis, chronic rhinosinusitis, eosinophilic otitis media, bullous pemphigoid, contact dermatitis, mastocytosis) with promising results.” *Id.*, 1-2; *see also* EX1044, abstract; EX1045, abstract.

72. IgE, as one of the critical mediators in food allergy, was a known target for such therapeutic intervention. EX1037, 4.

1. Omalizumab for the Treatment of Asthma and CRSwNP

73. XOLAIR (omalizumab) was approved in 2003 for the treatment of moderate to severe persistent asthma in adults and adolescents aged 12 and older (EX1050) and in 2016 for the treatment of moderate to severe persistent asthma in pediatric patients age six to less than twelve years of age, with weights as low as 20 kg and pre-treatment serum IgE of 30 to 1300 IU/mL (EX1051).

74. For asthma, the dosage amount and frequency of omalizumab were based on the total serum IgE (IU/ml) and body weight (kg) before administering omalizumab according to dosing charts, further discussed in Paragraphs 224, 232-244, below. The dosing charts explain which dosing regimen (dose and frequency) are appropriate depending on those two values. EX1007, 4-5. *PI2021* instructs, for asthma, using serum total IgE level (IU/mL) measured before the start of treatment and body weight (kg): “Determine dose (mg) and dosing frequency by serum total IgE level (IU/mL) measured before the start of treatment, and by body weight (kg).” EX1007, 3.

75. By 2021, omalizumab was commercially available in a pre-filled syringe containing either 75 mg/0.5 mL or 150 mg/mL solution. EX1007, 1, 34. As a result, omalizumab was administered in dosages with 75 mg increments, i.e.,

75, 150, 225, 300, etc. *See id.*, 4-6 (asthma and polyps dosing tables with doses of 75, 150, 225, 300, 375, 450, 525, and 600 mg). Consistent with the dosing tables, the label further states that the recommended dosage of XOLAIR, for asthma, is 75 to 375 mg every two or four weeks, depending on the patient's pre-treatment weight and IgE levels. EX1007, 4.

76. The omalizumab dosing tables for asthma and polyps were developed based on an algorithm factoring in pretreatment weight and IgE levels. EX1027, 1, 2. *Zhu's* first named author is from Genentech, the maker of XOLAIR. That Genentech author stated that: "The dosing table [for polyps] was based on the same algorithm as the allergic asthma dosing tables – at least 0.016 mg of omalizumab per kg of body weight per international unit of baseline IgE per mL per 4 weeks, to reduce the mean free IgE for patients to approximately 25 ng/mL or lower, with most patients achieving free IgE <50 ng/mL." EX1027, 2. In addition, *PI2021* further indicates that adult and adolescent patients 12 years of age and older were treated in a first clinical trial "according to a dosing table to administer at least 0.016 mg/kg/IU (IgE/mL) of XOLAIR ... over each 4-week period." EX1007, 24; *see also* EX1027, 2. Using that algorithm, one would calculate the dose per four weeks as follows:

Dose (mg) per 4-weeks	=	At least 0.016 mg x body weight (kg) x pretreatment IgE (IU/mL)
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77. Other prior art references also disclose using that formula to generate a dose, with respect to approved uses of omalizumab (asthma and nasal polyps). *See* EX1028, 68 (“the recommended monthly dose is equal to 0.016 mg x body weight (kg) x IgE levels (IU/mL)”); EX1017, 6 (omalizumab dosage for children 2-3 years of age at high-risk for developing asthma calculated to ensure “at least 0.016 mg/kg/IU total IgE (measured at screening) in 75 mg increments”); EX1031, 1309 (“The dose of study drug (omalizumab or placebo) administered was a minimum of 0.016 mg/kg/IgE (IU/mL) every 4 weeks; those requiring more than a 300-mg dose had their dose divided and given every 2 weeks.”); EX1046, 50-51 (dose of approximately 0.016 mg/kg per IU/ml of IgE can reduce free IgE by 89-99% in patients with allergic asthma and allergic rhinitis).

78. *PI2021* further states that “[t]here were no effects on fertility and reproductive performance in male and female *Cynomolgus* monkeys that received XOLAIR at subcutaneous doses up to 75 mg/kg/week.” EX1007, 24.

79. Based on the information in *PI2021*, a POSA would have understood that the FDA had approved omalizumab as being safe and effective for treating

asthma subjects weighing as little as 20 kg, with pretreatment total serum IgE as high as 1300 IgE, at doses of 75 to 375 mg every two to four weeks.

80. A POSA would have been aware that *Lowe* used PK/PD modeling and simulations and pooled analysis of safety data to conclude that the safety and efficacy of omalizumab are not impacted by whether a dose is administered once every four weeks or split such that half the dose is given every two weeks. *See* EX1052, 76. More specifically, *Lowe* states the following:

PK–PD modeling and simulation, together with pooled analyses of safety data, suggests that those patients currently receiving omalizumab at doses of 225 or 300 mg every 2 weeks will be able to switch to omalizumab 450 and 600 mg, respectively, every 4 weeks, without compromising safety or efficacy. Whether the sequence of actions is driven by omalizumab arriving at the effector site from the blood, or is indirect via free IgE suppression, or via inhibition of effector cells, or even combinations of these mechanisms, is immaterial to the point in question that 300 mg q2w and 600 mg q4w will translate to comparable steady-state concentrations of drug, the same steady-state concentrations of free IgE and the same steady-state downstream effector cell desensitization, and hence the same clinical response.

Id.

81. A POSA also would have known about several other studies that demonstrated the safety of omalizumab for treating asthma in patients less than 20 kg or six years of age. I discuss some of those studies below.

82. *Phipatanakul* disclosed a study of omalizumab in children 2-3 years of age at high-risk for developing asthma, with dosage based on ensuring at least

0.016 mg/kg/IU total IgE (measured at screening), using 75 mg increments.

EX1017, 3, 6. *Phipatanakul* explained that that FDA granted the Investigational New Drug (IND) down to two years based on over a decade of real world omalizumab safety data. *Id.*, 19. *Phipatanakul* further stated that epinephrine auto injectors would be provided to the families of subjects, including injectors for subjects weighing <15 kg. EX1017, 6.

83. While *Phipatanakul* does not provide the weights of its subjects, those weights can be approximated by using average height-weight tables. Based on such tables, a POSA would have expected omalizumab to be safe for administration to children as young as two years of age, on average weighing 11-12 kg. *See* EX1013; EX1015.

84. *Kopp* reports on a double-blind placebo controlled trial of 627 children from 6 to 12 years of age with a history of exacerbations and asthma symptoms regardless of treatment with inhaled corticosteroids to whom omalizumab or placebo were administered for 52 weeks. EX1038, 102. Subjects treated with omalizumab had 31% and 43% fewer clinically significant asthma exacerbations at 24 and 52 weeks, respectively. *Id.* Omalizumab also significantly reduced severe exacerbations in the subjects. *Id.* According to *Kopp*, the “authors concluded that add-on therapy with omalizumab is effective and well-tolerated as

maintenance therapy in children with moderate to severe, persistent, IgE-mediated asthma.” *Id.*

85. A POSA would have been aware that patients with allergic asthma often have comorbidities, including food allergies, and allergic asthma and food allergies are IgE mediated. EX1045, abstract.

86. A POSA also would have been aware that allergic asthma “is the most common noncommunicable disease in children worldwide.” EX1047, 1. At least 90% of children with asthma were known to have underlying allergies that were confirmed by IgE mediated aeroallergen sensitivity. *Id.*

87. A POSA would have been aware that a genetic predisposition to the production of IgE, atopy, is the underlying cause of most cases of asthma. EX1046, 49.

88. For the above reasons, a POSA would have understood that targeting IgE is not only a strategy for treating allergic asthma and rhinitis, but also for other IgE-mediated conditions, such as food allergies. *Id.*, 55; EX1006, 287; EX1028, 72

89. *Zhu* states that omalizumab dosing table used for nasal polyps is based on the same algorithm as used for the omalizumab allergic asthma dosing table. EX1027, 2. *Zhu* describes that algorithm as follows: “at least 0.016 mg of omalizumab per kg of body weight per international unit of baseline IgE per mL

per 4 weeks, to reduce the mean free IgE for patients to approximately 25 ng/mL or lower, with most patients achieving free IgE <50 ng/mL.” *Id.* *Zhu* examined pK/PD data for the treatment of asthma and polyps (CRSwNP) and found that “omalizumab PK and its effects on IgE were consistent between asthma and CRSwNP.” *Id.*, 10. *Zhu* concluded that the totality of the results “supports the appropriateness of the baseline body weight- and baseline IgE-based omalizumab dosing table used in the POLYP 1 and POLYP 2 [CRSwNP] studies, which are identical to the currently approved EU SmPc omalizumab asthma dosing table for patients with body weight 30 kg and higher.” *Id.*

90. *Zhu*’s finding that omalizumab PK and its effects on IgE are consistent between asthma and CRSwNP supports the conclusion that for IgE-mediated conditions, including food allergy, appropriate doses can be determined based on the asthma algorithm (at least 0.016 mg of omalizumab per kg of body weight per international unit of baseline IgE per mL per 4 weeks).

2. Impact of Omalizumab on Food Allergy in Patients Treated for Asthma

91. *Fiocchi 2019* describes an observational study that assessed the real-life effects of omalizumab on food threshold tolerability in children with food allergies who were being treated for severe atopic asthma (*i.e.*, allergic asthma). EX1029, 1901. “Fifteen children, allergic to 37 foods, were evaluated.” *Id.* *Fiocchi 2019* states that “[w]hen used in severe asthma, omalizumab induces a

significant increase in food tolerance thresholds” and that “[t]his reduces the risk of food reactions, allows for the safe introduction of some foods, and increases the quality of life of children with concomitant food allergy.” EX1029, 1901; EX1006, 288-289 (stating the following about the results seen in *Fiocchi 2019*: “After 4 months of Omalizumab treatment, all patients experienced an increase in their eliciting threshold to each food tested” and that the results represented “a statistically significant improvement for egg, milk, baked milk, and wheat.”).

92. Based on *Fiocchi 2019*, a POSA would have expected that the omalizumab treatment regimen for asthma, based on subject weight and pre-treatment total serum IgE, would also be effective for treating food allergies. Moreover, as discussed below, a POSA also would have been aware of over a decade of studies evaluating omalizumab for treating food allergies. *See* Paragraphs 93-122.

3. Omalizumab for the Treatment of Food Allergy

93. The prior art taught the use of omalizumab for the treatment of food allergy, in conjunction with OIT or as a monotherapy.

a) Proof of Concept for Using Anti-IgE Antibody for the Treatment of Food Allergy

94. In 2003, *Leung* reported on the results of a double-blind, randomized, dose-ranging trial in 84 patients with a history of immediate hypersensitivity to peanut, in which patients were randomized to receive 150, 300, or 450 mg of TNX-

901, a humanized IgG1 monoclonal antibody against IgE, or placebo. EX1049, Abstract. TNX-901 is also known as tazilumab. EX1030, 1011.

95. *Leung* concluded that “[a] 450 mg dose of TNX-901 significantly and substantially increased the threshold of sensitivity to peanut on oral food challenge from a level equal to approximately half a peanut (178 mg) to one equal to almost nine peanuts (2805 mg), an effect that should translate into protection against most unintended ingestions of peanuts.” EX1049, 986.

96. While *Leung* was a “basilar proof-of-principle study” for the use of IgE neutralization to treat food allergy, TNX-901 was not developed into a commercial drug. EX1030, 1011.

97. *Fiocchi 2021* reported “Almost 20 years ago the first anti-IgE antibody, Tazilumab (TNX-901), was shown to be able to increase the reactivity threshold to peanut after 2–4 weeks of treatment. Although that molecule was then no longer developed, but was replaced by Omalizumab and recently by Ligelizumab, this remains a basilar proof-of-principle study. Omalizumab is the most widely studied molecule for the treatment of food allergy.” EX1030, 1011.

b) Omalizumab plus OIT for the Treatment of Food Allergy

98. In 2014, *Bégin* reported on the results of a Phase 1 study of safety and tolerability in a rush oral immunotherapy protocol to multiple foods using omalizumab. EX1009, 1. *Bégin* discloses a dosing table for the study with

subjects weighing as little as 15 kg and screening IgE of 30 to 1500 IU/mL. *Id.*, 10.s2, Table E2. *Bégin* concluded that the data from administration of omalizumab according to the product insert to subjects 4 years of age or older with multifood allergies “demonstrate that rush OIT to multiple foods with 16 weeks of treatment with omalizumab could allow for a fast desensitization in subjects with multiple food allergies.” *Id.*, Abstract, 2-3.

99. In 2016, *MacGinnitie* disclosed the results of a randomized, double-blind, placebo-controlled phase II clinical trial of omalizumab as an add-on to peanut allergy desensitization therapy in which omalizumab was administered once every two or four weeks to subjects weighing as little as 15-20 kg with baseline IgE of 30-2000 IU/mL. EX1008, 874, 877, 881e.3. After treatment and increasing the amount of allergen, 23 of 29 subjects in the omalizumab arm met the challenge of 2000mg, as compared to only 1 of 8 subjects on placebo, with desensitization sustained in 23 subjects 33 weeks after discontinuing omalizumab treatment. *Id.*, 877-878. *MacGinnitie* concludes that omalizumab facilitates rapid OIT of high-risk subjects with peanut allergy that is maintained even after discontinuing omalizumab treatment: “this study ... provides rigorous scientific confirmation that omalizumab can facilitate rapid OIT of high-risk subjects with peanut allergy that is maintained even after omalizumab treatment is discontinued.” *Id.*, 877.

100. In 2016, *Martorell-Calatayud* reported on omalizumab assisted OIT in 14 egg- or cow-milk-allergic patients with asthma comorbidity, ranging from 3-13 years of age, who were refractory to conventional OIT, *i.e.*, patients that “were unable to tolerate conventional OIT because of allergic reactions, exhibiting grade 3-4 anaphylactic symptoms.” EX1040, 1. A POSA would have known that the average weight of a three year old is about 14 kg. *See* EX1014; EX1016.

Omalizumab was dosed according to the package insert. EX1040, 1.

Desensitization began after the start of omalizumab treatment, with the induction phase lasting 18 weeks, in which only 28% (4) of the patients experienced mild allergic reactions. EX1040, 1-2. At the end of the induction phase, all patients had achieved complete desensitization. *Id.*, 2. The authors found that “[a]ssociation of omalizumab allows safe and effective desensitization treatment in patients who have been refractory to it,” and conclude that “[s]afer OIT would allow OIT to become widely available to patients with food allergy and association with omalizumab could be the key to opening that door.” *Id.*, 3.

101. In 2017, *Takahashi* reported on a study of the use of omalizumab in combination with OIT for inducing desensitization in subjects 6-14 years of age with a high-risk cow’s milk allergy. EX1039, Abstract. Sixteen subjects at high-risk for life-threatening anaphylaxis to cow’s milk took part in the study, with ten receiving omalizumab at doses based on a formula provided by Genentech. *Id.*,

Abstract, 5, 8. All ten treated subjects achieved desensitization, while none of the placebo children achieved desensitization. *Id.* The study was originally designed for 50 subjects, but was stopped prematurely in view of the overwhelming superiority of OIT in combination with omalizumab. *Id.* (“This prospective randomized controlled trial was intended for 50 participants but was prematurely discontinued due to overwhelming superiority of OMB combined with microwave heated OIT over [cow’s milk] avoidance.”)

102. In 2018, *Andorf 2018* reported on a pilot test looking at the safety and efficacy of treating multifold allergies with omalizumab and OIT. EX1022, 1. At the time of the study, it had already been shown that desensitization in subjects allergic to single foods could be rapidly achieved using OIT combined with omalizumab. *Id.*, 5. Omalizumab or placebo was administered to 48 participants, aged 4-15, along with multifold oral immunotherapy (“OIT”) to 2-5 foods from the list of cashew, walnut, hazelnut, almond, sesame, cow’s milk, hen’s egg, peanut, soy, and wheat. *Id.*, 6. The foods that were provided as of the multifold OIT were those foods to which the subject had a significant allergic reaction. *Id.*, 7-8. Subjects received subcutaneous omalizumab dosed per the product insert or placebo for 16 weeks, with multifold OIT starting at 8 weeks. *Id.*, 2, 3. *Andorf* concluded that the study demonstrated “that patients with multifold allergies can be safely and effectively desensitized to their offending foods with a combination

of multifood oral immunotherapy with omalizumab treatment.” *Id.*, 14. The omalizumab arm also provided increased safety, such as reductions in gastrointestinal and respiratory symptom, as well as shorter times to reach maintenance dosing of the OIT. *Id.*, 7.

103. In a 2019 follow-up, *Andorf 2019* reported further that “desensitization with omalizumab-facilitated multifood OIT (up to 5 allergens) can be achieved in the majority of participants at multiple clinical sites within 30 weeks,” demonstrating that “omalizumab-facilitated multifood-OIT can be performed in multiple centers with a standardization protocol in a safe manner, with a high rate of completion.” EX1048, 28. *Andorf 2019* concluded that sustained desensitization was achievable, improving participants’ quality of life. *Id.*

c) Omalizumab Monotherapy for the Treatment of Food Allergy

104. In 2010, I and others published the results of a prospective pilot study to assess the efficacy of omalizumab in 22 patients with persistent asthma and concomitant IgE-mediated food allergy. EX1023, Abstract. Each of the patients were being treated with omalizumab and also had concomitant food allergies. *Id.*, 76, 82. We conducted the study, at least in part, because food allergen avoidance is difficult for children, and because accidental exposure to food allergens “is common, unpredictable, and, on rare occasion, can be fatal.” *Id.*, 76. I believe this

was one of the first, if not the first, publications evaluating the use of omalizumab for treatment of food allergies.

105. The patients received 150-300 mg omalizumab every two weeks or every four weeks for at least a year. EX1023, 82. These doses were chosen as they were the doses of omalizumab that our clinic used. “The patients’ allergic reactions to sensitized foods were compared before and after omalizumab treatment.” *Id.*

106. While the study was not blinded, and while the patients were not given controlled amounts of food allergens, “each patient consumed enough food allergen to be aware of their consumption and noticed an improvement when compared with their usual reaction to a similar amount of food.” *Id.*

107. We concluded that while asthma patients were treated with omalizumab, they “subjectively observed a reduction in their concomitant IgE-mediated food allergy symptoms,” with omalizumab appearing to decrease sensitivity to various food allergens. *Id.*, 83. We further concluded that “for patients who are at significant risk of severe or fatal food anaphylaxis, omalizumab may have a therapeutic role.” *Id.*

108. A 2011 poster from Peloché et al. (“*Peloché Poster*”) described the use of omalizumab treatment as an alternative to an elimination diet. EX1024. *Peloché Poster* described treating ten patients over the age of six who had IgE-

mediated allergy to milk or egg, anaphylaxis history, positive skin prick tests and specific IgE levels against certain foods. The patients received treatment with omalizumab for 16 weeks “without any significant adverse reaction.” After the 16 weeks of omalizumab treatment, eight of the patients underwent a single blind food challenges (SBFC). Eight patients underwent the blind food challenge, with four demonstrating complete tolerance, and all patients reaching a higher dose threshold than baseline. *Id.* The authors concluded that “[a]nti-IgE therapy has proven an effective and safe measure in the treatment of the persistent and severe allergy to milk and egg, whether used as monotherapy or as an adjuvant measure to the process of desensitization to food, making it safer and faster procedure.” *Id.* A 2011 Abstract from Peloché et al. reports on the same study/results and reports the same conclusion. EX1025.

109. *Sampson* is a 2011 letter to the editor that describes a phase II, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial designed to assess “the efficacy of omalizumab in reducing the risk of peanut-induced allergic reactions by comparing the amount of peanut tolerated without symptoms before and after treatment.” EX1031, 1309. Although the study was supposed to enroll 150 subjects, the study was stopped early due to two anaphylactic adverse events that occurred during oral food challenges conducted before administering omalizumab. The authors noted, however, that favorable

trends were seen in the patients treated with omalizumab, *i.e.*, the reason for halting the study early had nothing to do with the safety or efficacy of omalizumab. *Id.*

110. Regarding the dose of omalizumab used in the study, *Sampson* states: “The dose of study drug (omalizumab or placebo) administered was a minimum of 0.016 mg/kg/IgE (IU/mL) every 4 weeks; those requiring more than a 300-mg dose had their dose divided and given every 2 weeks.” *Id.*

111. Fourteen subjects, aged 6 to 75 completed the study before it was stopped. Seven subjects who completed the study were 6 to <13 years of age, five of whom received omalizumab. *Id.* Eight of the nine omalizumab-treated subjects who completed the study saw increases in peanut protein tolerability of greater than ten-fold, with the average increase for omalizumab treated patients reported as over 80-fold. *Id.*, 1310. The authors also concluded: “on the basis of this relatively limited data set, the omalizumab safety profile in the population with peanut allergy is consistent with previous experience in the populations with asthma and allergic rhinitis.” *Id.*, 1309.

112. *Savage* was published in 2012 and describes a study in which fourteen subjects with peanut allergy were treated with omalizumab for six months. The subjects’ threshold dose of peanut inducing allergic symptoms increased over 80-fold, from 80 to 6500 mg ($P < 0.01$). EX1032, 1 (Abstract).

113. In 2014, Nilsson et al. provided a case report regarding omalizumab treatment of five children, aged 6-16, with milk allergy diagnosed following severe reactions, including anaphylaxis. EX1036, 258. Omalizumab was dosed based on patient weight and serum IgE concentration according to the recommended doses for allergic asthma. *Id.* Basophil allergen threshold sensitivity (CD-sens) was used to monitor omalizumab treatment effects. *Id.*, Abstract. After four months of omalizumab treatment, four of the patients had negative CD-sens and negative milk challenges. The fifth patient required doubling of the omalizumab dose before achieving a negative CD-sens and a negative milk challenge. *Id.*, Abstract. The authors concluded that “Omalizumab appears useful in treatment of severe food allergy, e.g., anaphylaxis to milk.” *Id.*

114. In 2017, Mennini et al. (“*Mennini*”) described a study conducted “[t]o evaluate the effect of Omalizumab on food allergy in children with severe asthma.” EX1010, 15 (A42). *Mennini* indicated that six patients, from about age 7 to 21, “with severe asthma and anaphylactic reactions to two or more foods” were enrolled in the study and received omalizumab (150, 300, or 450 mg) every two-four weeks, and underwent a food challenge two to four weeks after the fourth dose. *Mennini* reported that “[a]fter treatment, 5/6 patients developed full tolerance to at least one specific food” and that the sixth patient showed 85% and 82% increases in tolerance to milk and egg, respectively. *Mennini* concluded that

omalizumab “significantly and substantially increased the threshold of sensitivity to foods on oral challenge” and that “[t]his effect should translate into protection against most unintended ingestions of food allergens. *Id.*

115. In *Fiocchi 2019* (discussed in Paragraphs 91-92, above), omalizumab was being used to treat severe atopic asthma, and the authors examined the impact of omalizumab on 15 subjects who were also allergic to at least two food.

EX1006, 288; EX1029, 1901. After treatment for four months, these 15 patients all demonstrated an increase in their eliciting threshold for the food allergen, and 9 could tolerate a full serving of the offending food. EX1006, 288; EX1029, 1905; EX1020.

116. In 2021, *Crespo* reported on a study wherein “the objective of the study was to describe the effect of omalizumab treatment in children diagnosed with [multiple food allergies] who experienced frequent anaphylactic reactions and the impact on their quality of life.” EX1018, 15 (Abstract). The subjects were children diagnosed with multifood allergies who also presented with anaphylaxis, aged 4.5 to 8.25 years of age, who weighed 17-28 kg and had pre-treatment total serum IgE of 205–1289 IU/mL. *Id.*, 20. After treatment with omalizumab, the subjects did not show reactions to most of the foods to which they previously had anaphylactic reactions. *Id.*, 15 (Abstract). The subjects were thus able to improve

their quality of life, expand the variety of their diet, and also avoid anaphylaxis due to inadvertent intake of foods to which they are allergic. *Id.*, 15-16 (Abstract).

117. In 2021, *Arasi*, a review article, taught that the data from early clinical trials demonstrated that omalizumab by itself could provide desensitization to one or multiple foods without the need to expose the subject to the allergen. EX1006, 286. *Arasi* summarizes findings from the most relevant studies of using omalizumab as a monotherapy, *Sampson* (EX1031), *Savage* (EX1032), and *Fiocchi 2019* (EX1029). *Id.*, 288 (Table 1). Further discussion of *Arasi* is provided below in Paragraphs 131-138.

d) Omalizumab is Safe for the Treatment of Food Allergy

118. As explained above, by 2021, the safety of omalizumab had been extensively demonstrated in many studies, including in pediatric patients. *See, e.g.* EX1043, 1; EX1046, 56-57; EX1007; EX1017, 19; EX1022, 7; EX1025.

119. In August 2018, FDA granted Genentech and Novartis Breakthrough Therapy Designation (BTD) for omalizumab for the prevention of severe allergic reaction to the accidental exposure to one or more foods in people with allergies to one or more foods. EX1011. Genentech's press release at the time noted that the designation was a result of "data from seven clinical studies over the last decade assessing the efficacy and safety of [omalizumab] against a range of food allergens, including peanut, milk, egg and others. These studies of [omalizumab],

as monotherapy or in combination with oral immunotherapy (OIT), were supported by Genentech and independent sponsors including the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH).”

EX1011, 1. To qualify as a breakthrough therapy in 2018, the FDA explained:

Breakthrough Therapy designation is a process designed to expedite the development and review of drugs that are intended to treat a serious condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s).

To determine whether the improvement over available therapy is substantial is a matter of judgment and depends on both the magnitude of the treatment effect, which could include duration of the effect, and the importance of the observed clinical outcome. In general, the preliminary clinical evidence should show a clear advantage over available therapy.

EX1012, 1.

120. The breakthrough therapy designation led to the initiation of a Phase 3 clinical trial titled: “Omalizumab as Monotherapy and as Adjunct Therapy to Multi-Allergen OIT in Food Allergic Participants (OUtMATCH).” EX1005, 1, 4.

The OUtMATCH study was sponsored by the NIAID, in conjunction with Genentech and Novartis. *Id.*. The multi-center, randomized, double-blind, placebo-controlled Phase 3 study was started in July 2019 and was open to participants aged 1 to less than 56 years of age who are allergic to peanut and at least two other foods. *Id.*, 4, 5.

121. Stage 1 of the study investigated whether “omalizumab [monotherapy] stops or decreases allergic reactions to peanut and other common food allergens after taking it for a length of time.” EX1005, 5. *OUtMATCH-V26* discloses that omalizumab will be administered “by subcutaneous injection either every 2 weeks or every 4 weeks for 16 to 20 weeks” and that “[t]he dose administered and the dosing interval are determined by serum total IgE level and body weight (measured before the start of treatment) per the study drug dosing table.” *Id.*, 6. *OUtMATCH-V26* further states that “[o]malizumab will be supplied in pre-filled syringes (PFS)” as “75 mg and 150 mg dosage forms.” *Id.*

122. Based on the inclusion criteria for *OUtMATCH-V26*, which included subjects as young as 1 year of age, a POSA would have understood that FDA viewed omalizumab as safe to administer to subjects 1 year of age or older. Other details regarding *OUtMATCH-V26* are discussed further below in Paragraphs 124-130.

VI. OVERVIEW OF THE PRIOR ART

123. The prior art that forms the primary basis for my opinions is summarized below, and further in Paragraphs 219-244.

A. NCT03881696: Omalizumab as Monotherapy and as Adjunct Therapy to Multi-Allergen OIT in Food Allergic Participants, Version 26 (*OUtMATCH-V26*; EX1005)

124. NCT03881696 is a clinical trial protocol sponsored by the NIAID, in conjunction with Genentech, Novartis, and Rho Federal Systems Division, Inc., titled “Omalizumab as Monotherapy and as Adjunct Therapy to Multi-Allergen OIT in Food Allergic Participants (*OUtMATCH*),” obtained from clinicaltrials.gov. EX1005, 1, 4; available at <https://clinicaltrials.gov/study/NCT03881696?term=outmatch&rank=1>. I have verified that a POSA searching for studies on “food allergy in children” and “omalizumab” would have readily found, among other studies, NCT03881696. In addition, a POSA searching for the “*OUtMATCH*” study or “NCT03881696,” both mentioned in *Arasi* (EX1006, 289, Figure 2), or using the link to *OUtMATCH/NCT03881696* identified in *Arasi* (*id.*, 289, Figure 2 and footnote 23), would have readily found NCT03881696. In this declaration I rely on Version 26 of the clinical trial, *OUtMATCH-V26*, which was published on ClinicalTrials.gov on May 2, 2022 (EX1005, 3, 4), and therefore was a printed publication available more than one year before *US959*’s earliest possible effective priority date of July 5, 2023. I was aware of ClinicalTrials.gov in the relevant time frame and had used it, in 2022 and earlier, to search for and locate clinical trial records. Moreover, NIH, which launched ClinicalTrials.Gov in 2000, described it

as “a consumer-friendly database ... with information on more than 4,000 federal and private medical studies involving patients and others at more than 47,000 locations nationwide” and stated that ClinicalTrials.gov “provides patients, families and members of the public easy access to information about the location of clinical trials, their design and purpose, criteria for participation, and, in many cases, further information about the disease and treatment under study.” EX1053, 1. In 2022 and earlier, ClinicalTrials.gov was well-known and POSAs routinely visited ClinicalTrials.gov to discover information about new therapies being investigated in clinical trials.

125. *OUtMATCH-V26* describes a multi-center, randomized, double-blind, placebo-controlled Phase 3 clinical trial with participants aged 1-55 years old who are allergic to peanuts and at least two other foods. EX1005, 5. *See* Paragraphs 227-229.

126. Stage 1 of the study investigated whether “omalizumab [monotherapy] stops or decreases allergic reactions to peanut and other common food allergens after taking it for a length of time.” *Id.*, 5.

127. *OUtMATCH-V26* discloses that omalizumab will be administered “by subcutaneous injection either every 2 weeks or every 4 weeks for 16 to 20 weeks” and that “[t]he dose administered and the dosing interval are determined by serum total IgE level and body weight (measured before the start of treatment) per the

study drug dosing table.” *Id.*, 6. Although the dosing table was not provided in *OUtMATCH-V26*, a POSA would have expected it to be like the dosing tables provided in *PI2021* and consistent with the dosing algorithm taught in the prior art, including in *PI2021*. See EX1027, 2; Paragraphs 76, 89-90, 238.

128. *OUtMATCH-V26* further states that “[o]malizumab will be supplied in pre-filled syringes (PFS)” as “75 mg and 150 mg dosage forms.” *Id.* Moreover, a POSA would have been aware that PFS dosage forms of XOLAIR for asthma and polyps were only supplied in 75 and 150 mg pre-filled syringes. EX1007, 34; See Paragraphs 75, 141, 236.

129. *OUtMATCH-V26* disclosed the following primary outcome: “Number of participants by Stage 1 Treatment Assignment, Omalizumab versus Placebo, Who Successfully Consume a Single Dose of ≥ 600 mg of Peanut Protein Without Dose-Limiting Symptoms During the DBPCFC [double-blind placebo-controlled food challenge] Conducted at the End of Treatment Stage 1.” EX1005, 9.

130. *OUtMATCH-V26* disclosed 95 secondary outcomes relating primarily to food challenge results at different times and the occurrence of adverse events. *Id.*, 9-31.

B. *Arasi* (EX1006)

131. Stefanie Arasi et al., *Omalizumab as monotherapy for food allergy*, 21 CURR. OPIN. ALLERGY CLIN. IMMUNOL. 286-291 (June 2021) (“*Arasi*”) was

published in June 2021, and therefore was a printed publication available more than one year before *US959*'s earliest possible effective priority date of July 5, 2023.

132. *Arasi* describes a need for therapies for patients with food allergies and states that “the most promising therapeutic options are oral immunotherapy (OIT) and biologicals; among the latter, Omalizumab is the most used either combined with OIT or as monotherapy.” EX1006, 286.

133. *Arasi* explains that Omalizumab is an anti-IgE humanized monoclonal antibody that “by binding to the IgE constant Cε3 region of free circulating IgE, prevents the latter from binding to the high-affinity FcεR1 receptors on effector cells (primarily basophils and mast cells), interfering with degranulation and release of pro-inflammatory mediators.” *Id.*

134. *Arasi* notes that omalizumab, due to its non-allergen specific inhibition of IgE/blockade of the immune response, is a potentially attractive candidate for IgE-mediated diseases, including food allergy: “The property of Omalizumab to induce not allergen-specific effects on allergic immune responses makes this biological treatment a potentially attractive candidate for several IgE-mediated diseases including food allergy.” *Id.*, 287.

135. *Arasi* states that omalizumab may be effective as a monotherapy for treating food allergy: “The current data from early stage clinical trials show that

Omalizumab may be effective by itself in providing desensitization to one or several foods without requiring allergen exposure as in oral immunotherapy.” *Id.*, 287.

136. *Arasi* summarizes the results of three studies (EX1031, EX1032, and EX1029) that evaluated the use of omalizumab monotherapy in food allergy and reported that patients experienced large, statistically significant increases in tolerated doses of food allergens compared to baseline. EX1006, 288 (summarizing “main findings” of EX1031, EX1032 (about 80-fold increase in tolerated dose), and of EX1029 (results represented “statistically significant improvement for egg, milk, baked milk, and wheat”).

137. With respect to dosing, *Arasi* states: “The majority of studies report on the administration of [omalizumab] with a dosage and a frequency (every 2 or 4 weeks) set based on the total serum IgE level and the weight of the individual patient, according to asthma and nasal polyps indications” and that “Omalizumab has been reported to be used also in subjects with total IgE up to 2,000 IU/mL without any specific safety concern.” EX1006, 289-290 (citing EX1008).

138. *Arasi* concluded, among other things, that “[t]he current evidence supports the use of Omalizumab, alone or combined with OIT, in allergic patients to provide desensitization to one or several foods.” *Id.* 290.

C. *PI2021* (EX1007)

139. *PI2021* is the July 2021 revision of the prescribing information for XOLAIR (EX1007, 1; https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/103976s5239lbl.pdf), available at <https://www.fda.gov/drugsatfda>, and therefore was a printed publication available more than one year before *US959*'s earliest possible priority effective date of July 5, 2023. *See* Paragraphs 18, 51, 158.

140. *PI2021* discloses the following omalizumab dosing tables, based on weight and baseline total serum IgE, for the treatment of asthma and polyps, with asthma subjects weighing as little as 20 kg and having baseline IgE of 30-1300 IU/mL.

Table 2. Subcutaneous XOLAIR Doses Every 2 or 4 Weeks* for Pediatric Patients with Asthma Who Begin XOLAIR Between the Ages of 6 to <12 Years

Summary of Dosing Recommendations Between All Ages 6 to 12 Years															
Pre-treatment Serum IgE (IU/mL)	Dosing Freq.	Body Weight													
		20-25 kg	>25-30 kg	>30-40 kg	>40-50 kg	>50-60 kg	>60-70 kg	>70-80 kg	>80-90 kg	>90-125 kg	>125-150 kg				
Dose (mg)															
30-100	Every 4 weeks	75	75	75	150	150	150	150	150	300	300				
>100-200		150	150	150	300	300	300	300	300	225	300				
>200-300		150	150	225	300	300	225	225	225	300	375				
>300-400		225	225	300	225	225	225	300	300	Insufficient Data to Recommend a Dose					
>400-500		225	300	225	225	300	300	375	375						
>500-600		300	300	225	300	300	375	Insufficient Data to Recommend a Dose							
>600-700		300	225	225	300	375	Insufficient Data to Recommend a Dose								
>700-800	Every 2 weeks	225	225	300	375	Insufficient Data to Recommend a Dose									
>800-900		225	225	300	375										
>900-1000		225	300	375											
>1000-1100		225	300	375											
>1100-1200		300	300												
>1200-1300		300	375												

*Dosing frequency:

- ☒ Subcutaneous doses to be administered every 4 weeks
- ☐ Subcutaneous doses to be administered every 2 weeks

Table 3. Subcutaneous XOLAIR Doses Every 2 or 4 Weeks* for Adult Patients with Nasal Polyps

Pretreatment Serum IgE (IU/mL)	Dosing Freq.	Body Weight							
		>30-40 kg	>40-50 kg	>50-60 kg	>60-70 kg	>70-80 kg	>80-90 kg	>90-125 kg	> 125-150 kg
		Dose (mg)							
30 - 100	Every 4 Weeks	75	150	150	150	150	150	300	300
>100 - 200		150	300	300	300	300	300	450	600
>200 - 300		225	300	300	450	450	450	600	375
>300 - 400		300	450	450	450	600	600	450	525
>400 - 500		450	450	600	600	375	375	525	600
>500 - 600		450	600	600	375	450	450	600	
>600 - 700		450	600	375	450	450	525		
>700 - 800	Every 2 Weeks	300	375	450	450	525	600		
>800 - 900		300	375	450	525	600			
>900 - 1000		375	450	525	600				
>1000 - 1100		375	450	600					
>1100 - 1200		450	525	600	Insufficient Data to Recommend a Dose				
>1200 - 1300		450	525						
>1300 - 1500		525	600						

*Dosing frequency:

☒	Subcutaneous doses to be administered every 4 weeks
☐	Subcutaneous doses to be administered every 2 weeks

EX1007, 5-6.

141. *PI2021* states that “[t]he recommended dosage for treatment of asthma is XOLAIR 75 mg to 375 mg by subcutaneous injection every 2 or 4 weeks based on serum total IgE level (IU/mL) measured before the start of treatment and by body weight (kg).” *Id.*, 4. *PI2021* also states that omalizumab is supplied as a PFS in only 75 mg and 150 mg prefilled syringes. *Id.*, 34. In addition, the doses of

omalizumab included in the dosing tables are in 75 mg increments, *i.e.*, 75 mg, 150 mg, 225 mg, 300 mg, 375 mg. *Id.*, 5-6.

142. In the asthma clinical trial, “[p]atients were treated according to a dosing table to administer at least 0.016 mg/kg/IU (IgE/mL) of [omalizumab] ... over each 4-week period” and the “[t]he maximum XOLAIR dose per 4 weeks was 750 mg.” *Id.*, 24.

D. MacGinnitie (EX1008)

143. Andrew J. MacGinnitie et al., *Omalizumab facilitates rapid oral desensitization for peanut allergy*, 139 J. ALLERGY CLIN. IMMUNOL. 873-881.e8 (2016) (“*MacGinnitie*”),” published in 2016, and therefore was a printed publication available more than one year before *US959*’s earliest possible effective priority effective date of July 5, 2023. *See* Paragraphs 18, 51, 158.

144. *MacGinnitie* discloses the results of a clinical trial of omalizumab in which the following omalizumab dosing table was used, with dosage amount/frequency based on subject weight and baseline total serum IgE.

TABLE E2. Dosing of omalizumab based on body weight and baseline total IgE level (mg study drug)

Dosing interval	Screening IgE (IU/mL)	Body weight (kg)								
		15-20 kg	21-25 kg	26-30 kg	31-40 kg	41-50 kg	51-60 kg	61-70 kg	71-80 kg	81-90 kg
Every 4 wk	30-100	75 mg	75 mg	75 mg	75 mg	150 mg	150 mg	150 mg	150 mg	150 mg
	101-200	150 mg	150	150	150	300	300	300	300	300
	201-300	150 mg	150	150	225	300	300			
	301-400	225 mg	225	225	300					
	401-500	225 mg	225	300						
	501-600	300 mg	300	300						
Every 2 wk	601-700	300 mg	300							
	201-300							225 mg	225 mg	225 mg
	301-400					225 mg	225 mg	225	300	300
	401-500				225 mg	225	300	300	375	375
	501-600				225	300	300	375	450	525
	601-700			225 mg	225	300	375	450	525	600
	701-800	225 mg	225 mg	225	300	375	450	450	600	*
	801-900	225 mg	225	225	300	375	450	525	*	*
	901-1000	225 mg	225	300	375	450	525	600	*	*
	1001-1100	225 mg	225	300	375	450	600	*	*	*
	1101-1200	300 mg	300	300	450	525	600	*	*	*
	1201-3000	300 mg	300	375	450	525	*	*	*	*
	1301-1500	300 mg	300	375	525	600	*	*	*	*
	1500-2000	375 mg	450	600	600	600	*	*	*	*

Asterisks denote parameters in which no study subject will be dosed with drug.

EX1008, 881.e3 (Table E2). Dosing based on weight would have required determining the subject's current weight before determining the appropriate dose.

145. Included in this table are doses of omalizumab, in 75 mg increments (*i.e.*, 75 mg, 150 mg, 225 mg, 300 mg, 375 mg), to be administered once every two weeks or once every four weeks for subjects weighing 15-20 kg with baseline IgE of 30-2000 IU/mL. EX1008, 881.e3 (Table E2).

146. *MacGinnitie* states that it “provides rigorous scientific confirmation that omalizumab can facilitate rapid OIT of high-risk subjects with peanut allergy.” EX1008, 877.

147. *MacGinnitie* discloses “[s]tudy drug [omalizumab] was administered by means of subcutaneous injection.” EX1008, 881.e1.

148. *MacGinnitie* discloses that “[t]he primary end point ... was the ability to tolerate a 2000-mg dose of peanut protein 6 weeks after stopping omalizumab or placebo injection. This was achieved in 23 of 29 subjects randomized to omalizumab (79% of the ITT population) and 23 (85%) of 27 who actually received peanut immunotherapy compared with 1 (12.5%) of 8 receiving placebo ($P < 0.01$ for the ITT population, Table II).” EX1008, 875, 878. These reductions in allergic reactions would have been observed after accidental exposure, just like they were observed after intentional exposure.

149. *MacGinnitie* states that approximately 20% of subjects undergoing OIT experience severe reactions requiring injection of epinephrine. EX1008, 874. *MacGinnitie* found that six of eight placebo-treated subjects had moderate reactions, while only 4 of 28 omalizumab-treated subjects had such reactions. *Id.*, 876.

E. *Bégin* (EX1009)

150. Phillipe Bégin et al., *Phase 1 results of safety and tolerability in a rush oral immunotherapy protocol to multiple foods using Omalizumab*, 10:7 ALLERGY ASTHMA & CLIN. IMMUNOL. 1-10s.3 (2014) (“*Bégin*”), was published in 2014, and therefore was a printed publication available more than one year before US959’s earliest possible effective priority date of July 5, 2023. *See* Paragraphs 18, 51, 158.

151. *Bégin* disclosed using omalizumab and OIT to treat human “[p]articipants with multiple food allergies.” EX1009, 1 (and 2, 5, Table E3). *Bégin* further disclosed that participants in the study could be four years or older, and that the actual subjects ranged from 4.5-15.4 years of age. *Id.*, 2, Suppl. Table E3. *Bégin* also disclosed that 17 of 25 subjects received OIT treatments with peanut and at least one or more of milk, egg, and cashew, meaning that 17 of the subjects were allergic to peanut and at least one or more of milk, egg, and cashew. EX1009, 2, Suppl. Table E3.

152. *Bégin* stated that omalizumab “was prepared and administered according to the product insert” and that “[o]malizumab injections were administered.” EX1009, 3. In 2014 (when *Bégin* was published), the XOLAIR label only included subcutaneous injection as the route of administration. EX1019, 2 (“Administer Xolair 150 to 375 mg by subcutaneous (SC) injection every 2 or 4 weeks.”).

153. *Bégin* discloses the results of phase 1 of a clinical trial of omalizumab in which the following omalizumab dosing table was used, with dosage amount/frequency based on subject weight and baseline total serum IgE.

Table E2- Omalizumab dosing according to weight and total IgE levels

Dosing Interval	Screening IgE (IU/mL)	Body weight (kg)/ Study drug dose (mg)								
Every 4 weeks		15-20 kg	21-25 kg	26-30 kg	31-40 kg	41-50 kg	51-60 kg	61-70 kg	71-80 kg	81-90 kg
	30-100	75 mg	75mg	75mg	75mg	150mg	150mg	150mg	150mg	150mg
	101-200	150 mg	150	150	150	300	300	300	300	300
	201-300	150 mg	150	150	225	300	300			
	301-400	225 mg	225	225	300					
	401-500	225 mg	225	300						
	501-600	300 mg	300	300						
	601-700	300 mg	300 mg							

Dosing Interval	Screening IgE (IU/mL)	Body weight (kg)/ Study drug dose (mg)								
Every 2 weeks		15-20 kg	21-25 kg	26-30 kg	31-40 kg	41-50 kg	51-60 kg	61-70 kg	71-80 kg	81-90 kg
	201-300							225mg	225mg	225mg
	301-400					225mg	225	225	300	300
	401-500				225mg	225	300	300	375	375
	501-600				225mg	300	300	375	450	525
	601-700			225mg	225	300	375	450	525	600
	701-800	225mg	225mg	225	300	375	450	450	600	*
	801-900	225mg	225	225	300	375	450	525	*	*
	901-1000	225mg	225	300	375	450	525	600	*	*
	1001-1100	225mg	225	300	375	450	600	*	*	*
	1101-1200	300mg	300	300	450	525	600	*	*	*
	1201-3000	300mg	300	375	450	525	*	*	*	*
	1301-1500	300mg	300	375	525	600	*	*	*	*

EX1009, Suppl. Table E2.

154. Included in this table are doses of omalizumab, in 75 mg increments (*i.e.*, 75 mg, 150 mg, 225 mg, 300 mg), to be administered once every two weeks or once every four weeks for subjects weighing 15-20 kg with baseline IgE of 30-1500 IU/mL. EX1009, Suppl. Table E2.

155. *Bégin* discloses that “[d]oses were determined based on weight and total IgE levels.” EX1009, 3, Suppl. Table E2. Dosing based on weight would

have required determining the subject's current weight before determining the appropriate dose.

156. *Bégin* disclosed that the secondary endpoints were: “i) the time to reach and maintain doses of 300 mg, 1000 mg and 4000 mg per food allergen protein as well as ii) a 10 fold increase from the baseline reactivity threshold to each of the food allergen proteins.” EX1009, 2.

157. *Bégin* stated that “this phase 1 study of rush mOIT provides initial preliminary evidence of increased dose tolerability.” *Id.* 6. These reductions in allergic reaction would have been observed after accidental exposure, just like they were observed after intentional exposure.

VII. ANALYSIS OF THE CHALLENGED CLAIMS

158. I have been told to assume that the earliest possible effective priority date for *US959* is July 5, 2023.

A. Claims 1, 3, 5, 17-18, and 22-24 are Anticipated by *MacGinnitie* (EX1008)

159. *MacGinnitie* disclosed every limitation of claims 1, 3, 5, 17-18, and 22-24 arranged as in the claims. *See* Paragraphs 143-149, 160-185.

1. Claim 1

160. Claim 1 of *US959* requires the following limitations:

(a) a method of treating a human subject having an allergy to a food allergen, the method comprising:

(b) administering to the subject by subcutaneous injection a pharmaceutical composition comprising a dose of omalizumab, wherein

(c) the subject weighs ≥ 10 kg to ≤ 15 kg, and

(d) has a total serum IgE level of ≥ 30 IU/ml to ≤ 1850 IU/ml, and

(e) wherein the dose is 150-225 mg every two weeks or 75-150 mg every four weeks.

161. Claim 1 recites the following alternative omalizumab dosing regimens:

(a) 150-225 mg every two weeks to subjects weighing ≥ 10 kg to ≤ 15 kg with a total serum IgE of ≥ 30 IU/ml to ≤ 1850 IU/ml; or

(b) 75-150 mg every four weeks to subjects weighing ≥ 10 kg to ≤ 15 kg with a total serum IgE of ≥ 30 IU/ml to ≤ 1850 IU/ml.

162. I was told that where a claim includes alternatives, anticipation exists when the prior art discloses each and every element of one alternative, *i.e.*, the prior art does not have to disclose each and every element of each and every alternative. This is consistent with my understanding of the term “or” as indicating alternative choices. *See* Paragraph 15.

163. A POSA would have understood that treating “a human subject” by administering omalizumab to “the subject” based on the body weight of “the subject” and the total serum IgE level of “the subject” encompasses a dosing

regimen for treating a single subject (“the subject”) with characteristics falling within the scope of the claim. I was told that anticipation exists if the prior art discloses that treatment of a single subject would entail practicing each and every element of only a single claim alternative. *See* Paragraph 23.

164. As explained below (Paragraphs 160-172), *MacGinnitie* disclosed a dosing table that when followed for a 15 kg subject with, for example, a baseline total serum IgE of 30-100, 101-200, or 701-800 IU/mL, meets every element of claim 1. EX1008, 881.e3.

(a) Treating a Human With a Food Allergy

165. *MacGinnitie* states that it “provides rigorous scientific confirmation that omalizumab can facilitate rapid OIT of high-risk subjects with peanut allergy.” EX1008, 887. Based on this disclosure, a POSA would have known that *MacGinnitie* disclosed a study in which omalizumab was used to treat human subjects with food allergies. Accordingly, *MacGinnitie* expressly disclosed treating a human with a food allergy.

(b) Administration of Omalizumab by Subcutaneous Injection

166. *MacGinnitie* disclosed that “[s]tudy drug [omalizumab] was administered by means of subcutaneous injection” (EX1008, 881.e1) and therefore expressly disclosed the subcutaneous injection element of claim 1.

(c) Subject Weight 10-15 kg

167. *MacGinnitie* disclosed a dosing table that included administering omalizumab to subjects weighing 15-20 kg, which includes administering omalizumab to a subject weighing 15 kg. EX1008, 881.e1. Accordingly, *MacGinnitie* expressly disclosed treating subjects within the claimed weight range.

(d) Subject Having Total IgE Serum Level of 30 – 1850 IU/ml

168. *MacGinnitie* discloses a subject inclusion criterion of “baseline ... total IgE level of 50 IU/L or greater but 2000 IU/L or less” (which a POSA would have understood as IU/ml)¹ and a dosing table that includes administering omalizumab to subjects weighing 15-20 kg with baseline/screening IgE of 30-2000 IU/mL. EX1008, 881.e1, .e3. The dosing table also includes several specific IgE ranges, including 30-100 IU/ml, 101-200 IU/ml, and 701-800 IU/ml, all of which are within the claimed range of baseline IgE, and the weight range of 15-20 kg would have included subjects weighing 15 kg. Accordingly, *MacGinnitie*

¹ A POSA would have understood that the references to “50 IU/L” and “2000 IU/L” were typographical errors because total IgE levels of 50 IU/L and 2000 IU/L, which correspond to 0.050 IU/mL and 2 IU/mL are very low and would not require treatment with an anti-IgE antibody.

expressly disclosed treating subjects within the claimed serum IgE range who are also within the claimed weight range.

(e) Dose of 150-225 mg Once About Every Two Weeks or 75-150 mg Once About Every Four Weeks

169. For a 15-20 kg subject, which includes a 15 kg subject, the *MacGinnitie* dosing table (excerpted below) disclosed administering 225 mg of omalizumab once every two weeks to, for example, a subject having a screening IgE of 701-800 IU/mL:

Every 2 wk	15-20 kg
201-300	
301-400	
401-500	
501-600	
601-700	
701-800	225 mg
801-900	225 mg

EX1008, 881.e3 (Table E2).

170. For a 15-20 kg subject, which includes a 15 kg subject, the *MacGinnitie* dosing table (excerpted below) disclosed administering 75 mg once every four weeks to a subject having a screening IgE of 30-100 IU/mL, and administering 150 mg once every four weeks to a subject having a screening IgE of 101-200 IU/mL.

Dosing interval	Screening IgE (IU/mL)
Every 4 wk	15-20 kg
	30-100 75 mg
	101-200 150 mg
	201-300 150 mg

EX1008, 881.e3 (Table E2).

171. For the above reasons, *MacGinnitie* expressly disclosed both of the dosage amount/frequency alternatives of claim 1 of *US959*.

172. For all of the above reasons, *MacGinnitie* disclosed every element of claim 1 and anticipated that claim.

2. Claims 3 and 5

173. Claims 3 and 5 depend from claim 1 and further limit the dosing amount/frequency and add that the total serum IgE level of the subject is determined prior to administration of a first dose of omalizumab. *See* Paragraph 49; EX1001, claims 3 and 5.

174. More specifically, claim 3 requires that omalizumab is administered once about every four weeks at a dose of 75 mg when baseline IgE is ≥ 30 and ≤ 300 IU/ml, and further requires that the total serum IgE level of the subject is determined prior to administration of a first dose of omalizumab.

175. Claim 5 depends from claim 1 and includes as one of its dosing alternatives that, for a subject with a body weight of >12 kg and ≤ 15 kg, the dose

of omalizumab is 75 mg once about every four weeks for a subject with a baseline total serum IgE of ≥ 30 and ≤ 300 IU/ml, and further requires that the total serum IgE level of the subject is determined prior to administration of a first dose of omalizumab.

176. For a 15-20 kg subject, which would include a 15 kg subject, the *MacGinnitie* dosing table (excerpted below) disclosed administering 75 mg once every four weeks to a subject having a screening IgE of 30-100 IU/mL.

Dosing interval	Screening IgE (IU/mL)	
Every 4 wk		15-20 kg
	30-100	75 mg
	101-200	150 mg
	201-300	150 mg

EX1008, 881.e3 (Table E2).

177. Furthermore, *MacGinnitie* disclosed that the dosage amount/frequency is based on the baseline/screening total serum IgE. *Id.* (“Dosing of omalizumab based on body weight and baseline total IgE level.”) A POSA would have understood that to use the baseline total serum IgE for dosing would have required determining the total serum IgE level of the subject prior to administration of a first dose of omalizumab.

178. For these reasons and the reasons explained with regard to claim 1, *MacGinnitie* disclosed every element of claims 3 and 5 and therefore anticipated those claims.

3. Claim 17

179. Claim 17 claims a method of treating a human subject having an allergy to a food allergen. Like claim 1, claim 17 requires administration by subcutaneous injection. Like claims 3 and 5, claim 17 requires that the total serum IgE level of the subject is determined prior to administration of a first dose of omalizumab. *See* Paragraph 49; EX1001, claim 17. For the same reasons as discussed above with respect to claims 1, 3, and 5, *MacGinnitie* expressly disclosed these elements of claim 17. *See* Paragraphs 160-178.

180. Claim 17 also includes different dosage amount/frequency alternatives, one of which is administering to the subject once about every four weeks a pharmaceutical composition comprising a dose of omalizumab of 75 mg for a subject with a total serum IgE of ≥ 30 and ≤ 300 IU/ml. EX1008, 881.e3.

181. For the same reasons as set forth above with respect to claim 3, *MacGinnitie* disclosed every element of at least one alternative in claim 17, and therefore anticipated claim 17. EX1008, 881.e3.

4. Claim 18

182. Claim 18 depends from claim 17 and further requires that the body weight of the subject is determined prior to administration of a first dose of omalizumab. *See* Paragraph 49; EX1001, claim 18. *MacGinnitie* disclosed that “dosing was based on weight and IgE level.” EX1008, 881.e1. A POSA would have understood that to base omalizumab dosing on weight, the weight of the subject would have to be determined prior to administration of a first dose of omalizumab. For this reason and those explained with regard to claim 17, *MacGinnitie* anticipated claim 18.

5. Claims 22-24

183. Claim 22 depends from claim 17 and further requires that the treating comprises reducing an allergic reaction following exposure of the subject to the food allergen. Claim 23 depends from claim 22 and further requires that “the exposure to the food allergen is accidental.” Claim 24 depends from claim 22 and further requires that “the allergic reaction is a moderate to severe allergic reaction.” *See* Paragraph 49; EX1001, claims 22-24.

184. *MacGinnitie* disclosed the following: “The primary end point ... was the ability to tolerate a 2000-mg dose of peanut protein 6 weeks after stopping omalizumab or placebo injection. This was achieved in 23 of 29 subjects randomized to omalizumab (79% of the ITT population) and 23 (85%) of 27 who

actually received peanut immunotherapy compared with 1 (12.5%) of 8 receiving placebo ($P < 0.01$ for the ITT population, Table II).” EX1008, 875, 878. Based on this disclosure, a POSA would have understood that the administration of omalizumab reduced an allergic reaction following exposure of the subject to the food allergen, and that this result would be observed after accidental exposure. For these reasons and the same reasons explained with regard to claim 17, *MacGinnitie* disclosed every element of claims 22 and 23 and anticipated those claims.

185. *MacGinnitie* states that “most subjects undergoing OIT experience allergic reactions during desensitization, with approximately 20% having severe reactions requiring injection of epinephrine and another 10% to 20% of patients being refractory to oral desensitization.” *Id.*, 874. *MacGinnitie* found that during initial rapid desensitization, 6 of 8 placebo-treated subjects “had significant (Bock grade 2) reactions,” while only 4 of 28 omalizumab-treated subjects had such reactions. *Id.*, 876. A Bock grade 2 reaction is moderate reaction. Accordingly, *MacGinnitie* disclosed that omalizumab reduced moderate-to-severe allergic reactions and therefore meets the added limitation of claim 24.

B. Claims 1, 3, 5, 17-18, and 22-24 are Obvious Over *MacGinnitie* (EX1008)

186. In addition to anticipating claims 1, 3, 5, 17-18, and 22-24 (Paragraphs 159-185), as explained below, in my opinion *MacGinnitie* renders those claims obvious (Paragraphs 187-190).

187. The dosing table in *MacGinnitie* (Table E2) includes omalizumab dosing amounts/frequencies for 15-20 kg patients (which includes a 15 kg patient) based on their baseline/screening total serum IgE. Based on the disclosures in Table E2, which expressly mention 15 kg patients, to the extent that *MacGinnitie* is not read as explicitly exemplifying treatment of a 15 kg patient, a POSA would have been motivated to use omalizumab to treat 15 kg patients and would have had a reasonable expectation of success when treating 15 kg patients with omalizumab in accordance with the disclosures of Table E2.

188. More specifically, based on Table E2, a POSA would have been motivated to administer omalizumab as follows, with a reasonable expectation of success:

- Administer 75 mg of omalizumab every four weeks to subjects weighing 15 kg and having a baseline/screening total serum IgE of 30-100 IU/mL;
- Administer 150 mg of omalizumab every four weeks to subjects weighing 15 kg and having a baseline/screening total serum IgE of 101-200 or 201-300 IU/mL; and
- Administer 225 mg of omalizumab every two weeks to subjects weighing 15 kg and having a baseline/screening total serum IgE of 701-800, 801-900, 901-1000, or 1001-1100 IU/mL.

189. In the table below, I summarize these three dosing regimens in the first three columns. In the fourth column I list the claims that would have been obvious to a POSA because the claim recites, either by itself or as one of the claimed dosing regimen alternatives, one of the above dosing regimens that a POSA would have been motivated to use based on Table E2 with a reasonable expectation of success.

Screening IgE (IU/mL)	Amount (mg)	Frequency	Claims Rendered Obvious
30-100	75	Every 4 weeks	1, 3, 5, 17-18, 22-24
101-200 201-300	150	Every 4 weeks	1
701-800 801-900 901-1000 1001-1100	225	Every 2 weeks	1

190. For the above reasons, including those in Paragraphs 159-185, *MacGinnitie* would have rendered claims 1, 3, 5, 17-18, and 22-24 obvious to a POSA.

C. Claims 1, 3, 5, 17-18, and 20-23 are Anticipated by *Bégin* (EX1009)

191. *Bégin* disclosed every element of claims 1, 3, 5, 17-18, and 20-24 arranged as in the claims. *See* Paragraphs 150-157, 192-211.

1. Claim 1

192. The elements of claim 1 are set forth above. *See* Paragraphs 49, 160; EX1001, claim 1. As explained below (Paragraphs 193-200), *Bégin* disclosed a dosing table that when followed meets every element of claim 1. EX1009, 10.E2.

(a) Treating a Human With a Food Allergy

193. *Bégin* disclosed using omalizumab and OIT to treat human “[p]articipants with multiple food allergies.” EX1009, 1 (and 2, 5, Table E3). Based on this disclosure, a POSA would have understood that *Bégin* disclosed a study in which omalizumab was used to treat human subjects with food allergies. Accordingly, *Bégin* expressly disclosed treating a human with a food allergy.

(b) Administration of Omalizumab by Subcutaneous Injection

194. *Bégin* disclosed that omalizumab “was prepared and administered according to the product insert” and that “[o]malizumab injections were administered.” EX1009, 3. In 2014 (when *Bégin* was published), the approved route of administration in the XOLAIR product insert was subcutaneous injection. EX1019, 2 (“Administer Xolair 150 to 375 mg by subcutaneous (SC) injection every 2 or 4 weeks.”) Accordingly, *Bégin* expressly disclosed the subcutaneous injection element of claim 1.

(c) Subject Weight 10-15 kg

195. *Bégin* disclosed a dosing table that included administering omalizumab to subjects weighing 15-20 kg, which includes administering omalizumab to a subject weighing 15 kg. EX1009, 10.E2. Accordingly, *Bégin* expressly disclosed treating subjects within the claimed weight range.

(d) Subject Having Total IgE Serum Level of 30–1850 IU/ml

196. *Bégin* disclosed a dosing table that included administering omalizumab to subjects weighing 15-20 kg (which includes subjects weighing 15 kg), with screening/baseline total IgE of 30-1500 IU/mL, which falls completely within the claimed range of 30-1850. EX1009, 10.E2. This would include subjects weighing 15 kg and having a baseline/screening total IgE of 30-100, 101-200, or 701-800. Accordingly, *Bégin* expressly disclosed treating subjects within the claimed serum IgE range who are also within the claimed weight range. *Bégin* therefore meets this element.

(e) Dose of 150-225 mg Once About Every Two Weeks or 75-150 mg Once About Every Four Weeks

197. For a 15 kg subject, the *Bégin* dosing table (excerpted below) disclosed administering 225 mg of omalizumab once every two weeks to, for example, a subject having a screening IgE of 701-800 IU/mL

Dosing Interval	Screening <u>IgE</u> (IU/mL)	Body weight (kg)/ Study drug dose (mg)
Every 2 weeks		15-20 kg
	201-300	
	301-400	
	401-500	
	501-600	
	601-700	
	701-800	225mg
	801-900	225mg

EX1009, 10.E2.

198. For a 15 kg subject, the *Bégin* dosing table (excerpted below) disclosed administering 75 mg once every four weeks to a subject having a screening IgE of 30-100 IU/mL, and administering 150 mg once every four weeks to a subject having a screening IgE of 101-200 IU/mL.

Dosing Interval	Screening <u>IgE</u> (IU/mL)	Body weight (kg)/ Study drug dose (mg)
Every 4 weeks		15-20 kg
	30-100	75 mg
	101-200	150 mg
	201-300	150 mg

EX1009, 10.E2.

199. For the above reasons, *Bégin* disclosed both of the dosage amount/frequency alternatives of claim 1 of US959.

200. For all of the above reasons, *Bégin* disclosed every element of claim 1 and anticipated that claim.

2. Claims 3 and 5

201. The elements of claims 3 and 5 are set forth above in Paragraphs 49, 173-175. *See* EX1001, claims 3, 5. As explained above, for a 15-20 kg subject, which would include a 15 kg subject, the *Bégin* dosing table (excerpted below) disclosed administering 75 mg once every four weeks to a subject having a screening IgE of 30-100 IU/mL for a 15 kg subject.

Dosing Interval	Screening IgE (IU/mL)	Body weight (kg)/ Study drug dose (mg)
Every 4 weeks		15-20 kg
	30-100	75 mg
	101-200	150 mg
	201-300	150 mg

EX1009, 10.E2.

202. Furthermore, *Bégin* disclosed that the dosage amount/frequency is based on the screening serum IgE. EX1009, 10.E2. A POSA would have understood that to use the screening serum IgE for dosing would have required determining the total serum IgE level of the subject prior to administration of a first dose of omalizumab.

203. For these reasons and the reasons explained with regard to claim 1, *Bégin* disclosed every element of claims 3 and 5 and therefore anticipated those claims.

3. Claim 17

204. The elements of claim 17 are set forth above in Paragraphs 49, 179-180. *See* EX1001, claim 17. Like claims 3 and 5, claim 17 requires that the total serum IgE level of the subject is determined prior to administration of a first dose of omalizumab. For the same reasons as discussed above with respect to claims 1, 3, and 5, *Bégin* disclosed these elements of claim 17. EX1009, 10.E2.

205. Claim 17 also includes different dosage amount/frequency alternatives, one of which is administering to the subject once about every four weeks a pharmaceutical composition comprising a dose of omalizumab of 75 mg for a subject with a total serum IgE of ≥ 30 and ≤ 300 IU/ml. EX1009, 10.E2.

206. For the same reasons as set forth above with respect to claim 3, *Bégin* disclosed every element of at least one alternative in claim 17, and therefore anticipated claim 17. *Id.*

4. Claim 18

207. The elements of claim 18 are set forth above in Paragraphs 49, 182. *See* EX1001, claim 18. Claim 18 depends from claim 17 and further requires that the body weight of the subject is determined prior to administration of a first dose

of omalizumab. *Bégin* disclosed that “[d]oses were determined based on weight and total IgE levels.” *Id.*, 10.E2. A POSA would have understood that to base omalizumab dosing on weight, the weight of the subject would have to be determined prior to administration of a first dose of omalizumab. For this reason and those explained with regard to claim 17, *Bégin* anticipated claim 18.

5. Claims 20-21

208. Claim 20 depends from claim 17 and further requires that the subject is from 1 year to 5 years of age. *See* Paragraph 49; EX1001, claim 20. *Bégin* disclosed that participants were eligible for inclusion if they were “older than or equal to 4 years old” and that the subjects ranged from 4.5-15.4 years of age. Accordingly, *Bégin* disclosed treating subjects from 1 year to 5 years of age. *Id.*, 2, 10.E3. For this reason and the same reasons as discussed above with respect to claim 17, *Bégin* disclosed every element of claim 20 and therefore anticipated claim 20.

209. Claim 21 depends from claim 17 and requires that the subject has an allergy to peanut and to one or more of milk, egg, and cashew. *See* Paragraph 49; EX1001, claim 21. *Bégin* disclosed that 17 of 25 subjects received OIT treatments with peanut and at least one or more of milk, egg, and cashew. *Id.*, 2, 10.E3. A POSA would have understood this to mean that 17 of the subjects were allergic to peanut and at least one or more of milk, egg, and cashew. For this reason and the

same reasons as discussed above with respect to claim 17, *Bégin* disclosed every element of claim 21, and therefore anticipated claim 21.

6. Claims 22-23

210. The elements of claims 22 and 23 are set forth above in Paragraphs 49, 183. *See* EX1001, claim 22-23. Claim 22 depends from claim 17 and further requires that the treating comprises reducing an allergic reaction following exposure of the subject to the food allergen. Claim 23 depends from claim 22 and further requires that “the exposure to the food allergen is accidental.”

211. *Bégin* disclosed the following: “The secondary endpoints (i.e. tolerability) were i) the time to reach and maintain doses of 300 mg, 1000 mg and 4000 mg per food allergen protein as well as ii) a 10 fold increase from the baseline reactivity threshold to each of the food allergen proteins.” *Id.*, 2. *Bégin* further states that “this phase 1 study of rush mOIT provides initial preliminary evidence of increased dose tolerability.” *Id.* 6. A POSA would have understood that “increased dose tolerability” means that after administration of omalizumab a subject can be exposed to a greater amount of food allergen with a reduced level of allergic response. Accordingly, a POSA would have understood that the administration of omalizumab reduced an allergic reaction following exposure of the subject to the food allergen, and that this result would be observed after accidental exposure. For these reasons, and the same reasons as discussed above

with respect to claim 17, *Bégin* disclosed every element of claims 22 and 23 and anticipated those claims.

D. Claims 1, 3, 5, 17-18, and 20-23 are Obvious Over *Bégin* (EX1009)

212. In addition to anticipating claims 1, 3, 5, 17-18, and 20-24 (*see* Paragraphs 192-211), as explained below, in my opinion *Bégin* renders those claims obvious (Paragraphs 213-216).

213. The dosing table in *Bégin* (Table E2) includes omalizumab dosing amounts/frequencies for 15-20 kg patients (which includes a 15 kg patient) based on their baseline/screening total serum IgE. Based on the disclosures in Table E2, which expressly includes 15 kg patients, to the extent that *Bégin* is not read as explicitly exemplifying treatment of a 15 kg patient, a POSA would have been motivated to use omalizumab to treat 15 kg patients and would have had a reasonable expectation of success when treating 15 patients with omalizumab in accordance with the disclosures of Table E2.

214. More specifically, based on Table E2, a POSA would have been motivated to administer omalizumab as follows, with a reasonable expectation of success:

- Administer 75 mg of omalizumab every four weeks to subjects weighing 15 kg and having a baseline/screening total serum IgE of 30-100 IU/mL;

- Administer 150 mg of omalizumab every four weeks to subjects weighing 15 kg and having a baseline/screening total serum IgE of 101-200 and 201-300 IU/mL; and
- Administer 225 mg of omalizumab every two weeks to subjects weighing 15 kg and having a baseline/screening total serum IgE of 701-800, 801-900, 901-1000, 1001-1100 IU/mL.

215. In the table below, I summarize these three dosing regimens in the first three columns. In the fourth column I list the claims that would have been obvious to a POSA because the claim recites, either by itself or as one of the claimed dosing regimen alternatives, one of the above dosing regimens that a POSA would have been motivated to use based on Table E2 with a reasonable expectation of success.

Screening IgE (IU/mL)	Amount (mg)	Frequency	Claims Rendered Obvious
30-100	75	Every 4 weeks	1, 3, 5, 17-18, 20-23
101-200 201-300	150	Every 4 weeks	1
701-800 801-900 901-1000 1001-1100	225	Every 2 weeks	1

216. For the above reasons, including those in Paragraphs 192-211, *Bégin* would have rendered claims 1, 3, 5, 17-18, and 20-23 obvious to a POSA.

E. Claims 1-29 are Obvious in view of the Combined Teachings of *OUtMATCH-V26* (EX1005), *Arasi* (EX1006), and *PI2021* (EX1007)

217. As explained below, based on the combined teachings of *OUtMATCH-V26*, *Arasi*, and *PI2021*, a POSA would have been motivated to practice the subject matter of claims 1-29 with a reasonable expectation of success. Accordingly, as explained below, claims 1-29 would have been obvious to a POSA in view of the combined teachings of over *OUtMATCH-V26*, *Arasi*, and *PI2021*.

218. As explained above, the claims of *US959* are directed to methods of treating low weight/young human subjects with a food allergy, comprising administering to the subject by subcutaneous injection a pharmaceutical composition comprising omalizumab, wherein the dose amount and frequency depend on the subject's weight (≥ 10 kg to ≤ 15 kg) and total serum IgE level (≥ 30 IU/ml to ≤ 1850 IU/ml).

1. A POSA Would Have Been Motivated to Find a Treatment for Food Allergy, Including in Infants and Young Children Weighing 10-15 kg

219. By July 2022, a POSA would have known that food allergy is a major and increasing problem, impacting over six million children and representing the main etiology of anaphylaxis in children, with estimates of over 40% of children with food allergies having experienced a severe allergic reaction requiring an emergency room visit, and food allergies resulting in an estimated 200,000

emergency room visits a year. EX1005, 5; EX1006, 286; EX1041, 65; EX1042; EX1021, 1; EX1011, 1; EX1018, 16; EX022, 2; EX1035, 1, 2; *see also* Paragraphs 54-57. “The risks of accidental exposures and life-threatening reactions can place a large burden on patients and their families” (EX1005,5), with estimated annual economic costs of billions of dollars. EX1009, 1; EX1006, 286; *see also* Paragraphs 55, 58. A POSA also would have known that the incidence of IgE-mediated forms of food allergy are typically rapid in onset and impact 1-10% of infants and pre-school aged children. EX1030, 1007; *see also* Paragraph 61. As of 2021, the standard of care for food allergy was allergen avoidance, but elimination diets were difficult and frustrating, especially for young children, and accidental exposures were frequent. EX1006, 286; *see also* Paragraphs 54, 104.

220. Based on all of the above, a POSA would have been motivated to find treatments for subjects, including in infants and young children, with established food allergies.

2. A POSA Would Have Been Motivated to Administer Omalizumab to Infants and Young Children with Food Allergies With a Reasonable Expectation of Safety and Efficacy

221. By July 2022, a POSA would have known that omalizumab is an IgE inhibitor, and that IgE inhibition reduces reaction to allergens and was a safe and effective treatment for allergic asthma. EX1007, 1. A POSA would have known that omalizumab binds to the constant region and thereby reduces the level of

circulating free IgE, regardless of allergen specificity. EX1038, 102, Fig. 1; EX1007, 286-287, Fig. 1; *see* EX1007, 22 (recommended doses of omalizumab for asthma reduced mean serum free IgE by over 96%); *see also* Paragraphs 66-69. Based on its mechanism of action, omalizumab was an attractive candidate for treating IgE mediated diseases, like food allergy. EX1038, 102, Fig. 1; EX1006, 287; EX1028, 72.

222. A POSA also would have been aware that omalizumab, when used to treat asthma patients, also treated their food allergies, as it resulted in “statistically significant improvement [in eliciting threshold] for egg, milk, baked milk, and wheat” and therefore would have known that IgE inhibition could also treat food allergy. EX1006, 288-289; EX1029; EX1030, 1011; *see also* Paragraphs 91-92.

223. By July 2022, omalizumab had been proven to be safe and effective for the treatment of moderate to severe asthma in patients as young as six years of age and weighing as little as 20 kg, with total serum IgE of 30 to 1300 IU/mL. EX1007, 5.

224. A POSA would have been aware that a dosing table based on subject weight (in kg) and pretreatment/baseline IgE (IU/mL) is used to determine the omalizumab (XOLAIR) dose amount/frequency for treating asthma, wherein the dose is 75 to 375 mg every two or four weeks in 75 mg increments. EX1007, 4, 5. A POSA would have known that the dosing table aims “to administer at least 0.016

mg/kg/IU (IgE/mL) of XOLAIR ... over each 4-week period,” in 75 mg increments, with a maximum one time dose of 15 mg/kg. EX1007, 24; *see also* Paragraphs 232-244.

225. As explained above, a POSA would have known about *Phipatanakul*, in which, based on over a decade of safety data, the FDA granted an IND down to two years of age with dosage based on ensuring at least 0.016 mg/kg/IU total IgE (measured at screening), using 75 mg increments. EX1017, 3, 6, 19; *see also* Paragraphs 81-83. A POSA would have understood this to mean that omalizumab was considered safe for subjects as young as two, who have average weights of 11-12 kg (*see* EX1013; EX1015), dosed to receive at least 0.016 mg/kg/IU total IgE (measured at screening), using 75 mg increments.

226. A POSA also would have been aware of many studies of omalizumab for the treatment of food allergy, both as a monotherapy and in combination with OIT, that demonstrated the safety and efficacy of omalizumab for treating food allergy, including in subjects under five years of age. *See* Paragraphs 93-122, 124-157, 227-228.

227. Studies of omalizumab in combination with OIT include the following:

- ***OUtMATCH-V26 (EX1005)***: May 2, 2022 version of clinical trial of omalizumab for the treatment of subjects with food allergies aged 1-55,

wherein the study had been ongoing for about 33 months as of May 2, 2022.

- ***Martorell-Calatayud (EX1040)***: Subjects 3-13 years of age with egg or cow milk allergy and asthma comorbidity (“[a]ssociation of omalizumab allows safe and effective desensitization treatment in patients who have been refractory to it”)
- ***Andorf 2018 (EX1022)***: Subjects 4-15 years of age (“patients with multifood allergies can be safely and effectively desensitized to their offending foods with a combination of multifood [OIT] with omalizumab treatment”); *see also Andorf 2019 (EX1048)*.
- ***Takahashi (EX1039)***: subjects 6-14 years of age with high risk for cow’s milk allergy (“trial was intended for 50 participants but was prematurely discontinued due to overwhelming superiority of OMB [omalizumab] combined with microwave heated OIT over [cow’s milk] avoidance.”)

228. Studies of omalizumab monotherapy include the following:

- ***OUtMATCH-V26 (EX1005)***: May 2, 2022 version of clinical trial of omalizumab for the treatment of subjects with food allergies aged 1-55, wherein the study had been ongoing for about 33 months as of May 2, 2022.

- *Sampson* (EX1031), *Savage* (EX1032), and *Fiocchi 2019*, all of which are discussed in *Arasi* (EX1006, 288):
 - ***Sampson* (EX1031):** omalizumab dosed to 6-12 year olds to achieve a minimum of 0.016 mg/kg/IgE every four weeks was found to have a safety profile consistent with previous experience in asthma.
 - ***Savage* (EX1032):** in omalizumab patients, threshold dose of peanuts to induce allergic symptoms increased by over 80-fold.
 - ***Fiocchi 2019* (EX1029):** patients with food allergies who received omalizumab to treat asthma saw increases in the eliciting threshold for their food allergens.

229. A POSA would have been aware of the *OUtMATCH-V26* study, in which it was intended to administer omalizumab as monotherapy and in combination with OIT, for the treatment of food allergy in subjects 1-55 years of age. EX1005, 5. The *OUtMATCH* study was started in July 2019, and was ongoing in May 2022, almost three years later. *See also* Paragraphs 124-130. A POSA would have understood, from the existence of this study, its inclusion of subjects as young as one year of age, and the fact that the study was ongoing for about three years, that FDA viewed omalizumab as safe for administration to subjects as young as one ear of age.

230. In addition, based on the studies referenced above (Paragraphs 227-228), a POSA would have understood that omalizumab is safe and effective for the treatment of food allergies, both in combination with OIT and as a monotherapy.

231. A POSA also would have been aware that in 2018, omalizumab was granted Breakthrough Therapy Designation for the treatment of food allergies: “Breakthrough Therapy Designation was granted on the basis of data from seven clinical studies over the last decade assessing the efficacy and safety of [omalizumab] against a range of food allergens including peanut, milk, egg and others.” EX1011, 1; *see also* Paragraphs 57, 119. A POSA would have understood that receiving BTB meant that the FDA had concluded that omalizumab treats a serious or life-threatening condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapies on at least one clinically significant endpoint. EX1012; *see also* Paragraphs 57, 119.

3. A POSA Would Have Known how to Determine the Dose Amount/Frequency Based on Subject Weight and Baseline IgE

232. *OUTMATCH-V26* taught the use of serum total IgE and body weight, per a dosing table, to determine omalizumab dosage. EX1005, 6. *OUTMATCH-V26* also taught that omalizumab would be administered “by subcutaneous injection every 2 weeks or every 4 weeks.” *Id.*

233. *Arasi* taught that the majority of omalizumab food allergy studies used a dosage/frequency (every 2 or 4 weeks) based on subject weight and total IgE “according to” the asthma and polyps indications. EX1006, 290.

234. *PI2021* taught that for treatment of asthma and polyps, omalizumab was administered every two weeks or every four weeks (EX1007, 4), wherein the dosage amount was in increments of 75 mg (*id.*, Table 1, 2, and 3, showing dosing amounts in 75 mg increments, *i.e.*, 75, 150, 225, 300, 375 mg).

235. Other prior art references also taught administering omalizumab every two or four weeks in increments of 75 mg for the treatment of food allergies. *See* EX1008, Table E2; EX1009, Table E2; *see also, e.g.*, Paragraphs 75, 82, 141, 144-145, 153-154.

236. *OUtMATCH-V26* and *PI2021* both taught that omalizumab would be supplied in 75 mg and 150 mg pre-filled syringes. EX1005, 6 (“[o]malizumab will be supplied in pre-filled syringes (PFS)” as “75 mg and 150 mg dosage forms”); EX1007, 34. In addition, *Phipatanakul* expressly taught dosing omalizumab in 75 mg increments: “at least 0.016 mg/kg/IU total IgE (measured at screening) in 75 mg increments” (EX1017, 6) ; *see also* Paragraph 82.

237. *PI2021* taught that “[p]atients were treated according to a dosing table to administer at least 0.016 mg/kg/IU (IgE/mL) of [omalizumab] ... over each 4-

week period.” EX1007, 24. A POSA would have understood that this meant calculating the dose of omalizumab for each four week period as follows:

Calculated Dose of Omalizumab per 4 Weeks

Calculated Dose (mg) per 4 Weeks	=	At least 0.016 mg x body weight (kg) x pretreatment IgE (IU/mL)
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238. Several other prior art references taught administration of omalizumab to treat asthma or food allergy wherein the dosage for each four week period was at least 0.016 mg/kg/IU (IgE/mL). *See* EX1028, 68 (“the recommended monthly dose is equal to 0.016 mg x body weight (kg) x IgE levels (IU/mL)”); EX1017, 6 (omalizumab dosage for children 2-3 years of age at high-risk for developing asthma calculated to ensure “at least 0.016 mg/kg/IU total IgE (measured at screening) in 75 mg increments”); EX1027, 2 (explaining that the dosing table for nasal polyps “was based on the same algorithm as the allergic asthma dosing tables - at least 0.016 mg of omalizumab per kg of body weight per international unit of baseline IgE per mL per 4 weeks, to reduce the mean free IgE for patients to approximately 25 ng/mL or lower, with most patients achieving free IgE <50 ng/mL.”); EX1031, 1309 (“The dose of study drug (omalizumab or placebo) administered was a minimum of 0.016 mg/kg/IgE (IU/mL) every 4 weeks; those requiring more than a 300-mg dose had their dose divided and given every 2

weeks.”); EX1046, 50-51 (dose of approximately 0.016 mg/kg per IU/ml of IgE can reduce free IgE by 89-99% in patients with allergic asthma and allergic rhinitis) ; *see also* Paragraph 77.

239. As explained above, *Arasi* and *PI2021* taught administering omalizumab every 2 weeks or every four weeks. To calculate the two-week dosage, a POSA would have divided the calculated four-week dose by 2.

Calculated Dose of Omalizumab per 2 Weeks (CMD2)

Calculated Dose (mg) per 2-Weeks	=	Calculated Dose (mg) per 4 Weeks / 2
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240. As explained below, a POSA also would have understood that the Calculated Dose per four weeks is the minimum dose to be administered every four weeks, and that the calculated dose per two weeks is the minimum dose to be every two weeks. *See* EX1007, 24 (“administer at least ...”); EX1017, 6 (ensure “at least ...”); EX1027, 2 (“at least ...”); EX1031, 1309 (“a minimum of ...”).

241. Because omalizumab was only supplied in 75 mg increments (EX1005, 6; EX1007, 34), *PI2021* taught administering omalizumab in 75 mg increments for the treatment of asthma and polyps (EX1007, 4, Tables 1-3), and other prior art taught administering omalizumab in 75 mg increments for treating food allergies (*see, e.g.*, 1008, 1009), a POSA would have been motivated to

increase the calculated two and four week doses to the next highest increment of 75 mg.

242. The following are examples of how a POSA would have determined four-week and two-week doses. Paragraphs 243-244.

243. As a first example, assume a patient weighing 12.5 kg with a baseline total serum IgE of 940 IU/mL. The four-week and two week doses are calculated as follows:

Calculated 4-Week Dose	=	At least 0.016 mg x 12.5 kg x 940 IU/mL = at least 188 mg
Calculated 2-Week Dose	=	At least 188 mg/2 = at least 94 mg

The appropriate four-week dose is 225 mg, because it is the next highest 75 mg increment after 188 mg. The appropriate two-week dose is 150 mg, because it is the next highest 75 mg increment after 94 mg. Thus, in this example, a patient weighing 12.5 kg with a baseline total serum IgE of 940 IU/mL would be administered either 225 mg every 4 weeks or 150 mg every 2 weeks.

244. As a second example, assume a patient weighing 13.5 kg with a baseline total serum IgE of 165 IU/mL. The four-week and two week doses are calculated as follows:

Calculated 4-Week Dose	=	At least 0.016 mg x 13.5 kg x 165 IU/mL = at least 35.6 mg
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Calculated 2- Week Dose	=	At least 35.6 mg/2 = at least 17.8 mg
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The appropriate four-week dose is 75 mg, because it is the next highest 75 mg increment after 35.6 mg. The appropriate two-week dose is also 75 mg, because it is the next highest 75 mg increment after 17.8 mg. Thus, in this example, a patient weighing 13.5 kg with a baseline total serum IgE of 165 IU/mL would be administered either 75 mg every 4 weeks or 75 mg every 2 weeks.

4. Claim 1 is Obvious over the Combined Teachings of *OUtMATCH-V26*, *Arasi* and *PI2021*

a) *OUtMATCH-V26* Teaches Every Limitation of Claim 1 Except the Specific Dosing Regimen Based on Patient Weight and Pre-Treatment/Baseline Serum IgE

245. *OUtMATCH-V26* teaches every limitation of claim 1 except the specific dosing regimen based on patient weight and pre-treatment/baseline total serum IgE. *See* Paragraphs 124-230. More specifically, *OUtMATCH-V26* taught:

- Administering omalizumab to treat human subjects having a food allergy (EX1005, 5 (“The primary objective of the study is to compare the ability to consume foods without dose-limiting symptoms during a double-blind placebo-controlled food challenge (DBPCFC), after treatment with either omalizumab or placebo for omalizumab.”));

- Subcutaneous administration (*id.*, 6 (“Eligible participants are randomized to receive omalizumab by subcutaneous injection either every 2 weeks or every 4 weeks for 16 to 20 weeks.”));
- Administering omalizumab every two weeks or every four weeks (*id.*);
- Administering incremental 75 and 150 mg unit doses (*id.*);
- Treating subjects 1-55 years of age (*i.e.*, 1 to less than 56 years of age), which a POSA would have understood includes subjects weighing ≥ 10 kg to ≤ 15 kg (*id.*, 5 (“This study is a multi-center, randomized, double-blind, placebo-controlled study in participants 1 to less than 56 years of age”));
- Dosing based on weight and pretreatment total serum IgE levels per a study dosing table (*id.*, 6 (“The dose administered and the dosing interval are determined by serum total IgE level and body weight (measured before the start of treatment) per the study drug dosing table.”)); and
- Determining total serum IgE prior to administering a first dose of omalizumab (*id.*).

246. *OUtMATCH-V26*, while teaching that dosing was based on weight and pretreatment IgE, that the single unit dosage forms were 75 mg and 150mg,

and that patients were dosed every 2 or every 4 weeks, does not teach the specifically claimed dosing regimen or provide the referenced study dosing table. As explained below, *Arasi* and *PI2021* taught the missing elements, and a POSA would have been motivated to combine the teachings of *OUtMATCH-V26*, *Arasi*, and *PI2021*, with a reasonable expectation of success.

- b) “A method of treating a human subject having an allergy to a food allergen, the method comprising: administering to the subject by subcutaneous injection a pharmaceutical composition comprising a dose of omalizumab”**

247. A POSA would have been aware of the need to treat food allergy in young patients and the fact that omalizumab had been shown to be safe and effective for the treatment of food allergy, and therefore would have been motivated to use omalizumab for the treatment of young children with food allergies. *See* Paragraphs 93-122, above.

248. *OUtMATCH-V26* (and other prior art) disclosed using omalizumab to treat human subjects with food allergies by administering omalizumab by subcutaneous injection. EX1005, 6; *see also* EX1008, 881e.1; EX1027, 2; *see* Paragraphs 124-130.

249. It would have been obvious to use a pharmaceutical composition comprising omalizumab because *PI2021* states that XOLAIR/omalizumab and excipients are supplied in a prefilled syringe. EX1007, 21.

250. A POSA would have been motivated to use the omalizumab composition taught in *PI2021* when treating the IgE mediated condition of food allergy as taught in *OUtMATCH-V26* with a reasonable expectation of success because, as taught in *PI2021*, such a composition had already been approved as safe and effective for treating another IgE mediated condition, asthma (EX1007, 1, 3), and because a POSA would have been aware that omalizumab had been shown to be safe for treatment of children (EX1017, 19) and had been shown to be effective for treating food allergy (Paragraphs 93-122).

251. For these reasons, it would have been obvious to a POSA to administer omalizumab subcutaneously for the treatment of food allergies.

c) Dosing Regimen Alternatives 1 and 2

252. Claim 1 recites two alternative dosing regimens, 150-225 mg every two weeks for subjects weighing 10-15 kg with a total serum IgE of 30-1850 IU/ml, or 75-150 mg every four weeks to subjects weighing 10-15 kg with a total serum IgE of 30-1850 IU/ml. As explained below, both of these alternative dosing regimens would have been obvious to a POSA.

- (1) Alternative 1: “wherein the pharmaceutical composition is administered once about every two weeks and the dose of omalizumab is from 150 mg to 225 mg ... and wherein body weight of the subject is equal to or greater than 10 kg and less than or equal to 15 kg, and total serum IgE level of the subject is equal to or greater**

than 30 IU/ml and less than or equal to 1850 IU/ml”

253. With respect to subject weight, *OUtMATCH-V26* studied patients ranging from 1 year to less than 56 years of age (*i.e.*, 1-55 years of age) in ten U.S. locations. EX1005, 5. 31, 33-35. A POSA would have been motivated to treat infants and young children with omalizumab because millions of children have food allergies and food allergies are the number one cause of emergency room visits for infants and children. *See, e.g.*, EX1005, 5; *see* Paragraphs 54-63, 219-220. In addition, a POSA would have been aware that based on over a decade of safety data, studies had been conducted in which omalizumab was administered to subjects as young as two years of age. EX1017, 6. A POSA therefore would have expected omalizumab to be safe for use in infants and young children weighing 10-15 kg; *see* Paragraphs 118-122, 221-231.

254. With respect to the weight range in the claimed dosing regimen for alternative 1, a POSA would have been aware of and had access to weight charts for boys and girls that provide the average weight of children at different ages. *See* EX1013-1016. Based on those charts, a POSA would have known that a 1-5 year old boys and girls in the 50TH percentile for weight have an average weight of about 10-18 kg. Accordingly, *OUtMATCH-V26* taught the treatment of subjects that would include 10-15 kg subjects.

255. With respect to the IgE range in the claimed dosing regimen for alternative 1, *PI2021* includes pediatric asthma dosing tables that teach dosing regimens for subjects with total baseline IgE of 30-1300 IU/mL. EX1007, 5 (Table 2). In addition, *Arasi* teaches that omalizumab had been safely administered in subjects with a total baseline IgE up to 2,000 IU/mL. EX1006, 290; *see also* EX1008, 881.e3 (omalizumab for food allergy in subjects weighing as little as 15 kg with baseline IgE of 30-2000 IU/mL). A POSA therefore would have understood that omalizumab could be used safely in subjects having an IgE of 30-2000 IU/mL, and therefore also could be used safely in subjects having an IgE within the claimed range of 30-1850 IU/mL. *See* Paragraphs 99, 145, 168.

256. As explained above (Paragraphs 124-142, 232-234, 245-246), *OUtMATCH-V26*, *Arasi*, and *PI2021* each teach the administration of omalizumab every two or four weeks, including for the treatment of food allergies. EX1005, 5, 6 (for treating food allergies); EX1006, 289-290 (for treating food allergies); EX1007, 5, 6 (for treating asthma and polyps).

257. As explained above (Paragraphs 232-237, 245-246), *OUtMATCH-V26* taught that in a clinical trial of omalizumab for the treatment of food allergy, the dose administered and the dosing interval would be determined by serum total IgE level and body weight (measured before the start of treatment) per a study drug dosing table. EX1005, 6. *Arasi* taught that the majority of studies on omalizumab

for treating food allergies determine the dosage and frequency (every 2 or 4 weeks) based on subject weight and total serum IgE, according to the asthma and nasal polyps indication. EX1006, 289-290. *PI2021* taught that in asthma clinical trials, “[p]atients were treated according to a dosing table to administer at least 0.016 mg/kg/IU (IgE/mL) of XOLAIR ... over each 4-week period.” EX1007, 24.

258. Based on the combined teachings of *OUtMATCH-V26*, *Arasi*, and *PI2021*, a POSA would have been motivated to calculate a minimum four week dosage using the formula in *PI2021*, and a minimum two week dosage by halving the four week dosage. See Paragraphs 232-244.

259. While the claims are directed to administering omalizumab to “a human subject,” each of the claims includes ranges of body weight and IgE that would encompass many subjects. A POSA would have known that subjects of any weight within the range of 10-15 kg could have any IgE between 30 and 1850 IU/ml, or the subject could have an IgE outside that range. A POSA also would have known that a subject having an IgE of 30-1850 could have any weight in the range of 10-15 kg, or a weight outside that range. Accordingly, for purposes of my analysis, for each alternative combination of weight range and IgE range I determined the weight and IgE for a hypothetical representative subject. I did so by averaging the endpoints of the claimed weight and IgE ranges. In my opinion,

such a “representative” subject is just as likely as any other weight/IgE combination within the claimed range.

260. For the alternative in which the subject weighs 10-15 kg with an IgE of 30-1850 IU/mL, a representative subject determined in this way would weigh 12.5 kg $(= (10+15)/2)$ and have an IgE of 940 IU/mL $(=(30+1850)/2)$.

261. For such a representative subject, the calculated four week dosage is at least 188 mg $(0.016 \times 12.5 \times 940)$ and the calculated two week dosage is at least 94 mg $(188/2)$.

262. As explained above (Paragraphs 232-244), because this is a minimum dose, and because *OutMATCH-V26* and *PI2021* teach that omalizumab is supplied in 75 and 150 mg pre-filled syringes, a POSA would have increased the calculated 4 and 2 week dosages up to the next 75 mg increment. Therefore, the 4 week dose would be 225 (the next 75 mg increment after 188 mg), and the 2 week dose would be 150 (the next 75 mg increment after 94 mg).

263. The four week dose of 225 mg is within the range of doses in alternative 1.

- (2) **Alternative 2: “wherein the pharmaceutical composition is administered ... once about every four weeks and the dose of omalizumab is from 75 mg to 150 mg, and wherein body weight of the subject is equal to or greater than 10 kg and less than or equal to 15 kg, and total serum IgE level of the subject is equal to or**

greater than 30 IU/ml and less than or equal to 1850 IU/ml”

264. The “alternative 2” dosing regimen has the same weight and IgE limitations as the alternative 1 dosing regimen for claim 1. Accordingly, with respect to the claimed weight and IgE ranges in alternative 2, the same reasoning applies as with respect to alternative 1. *See* Paragraphs 253-263.

265. Like alternative 1, a representative subject for alternative 2, determined by averaging the endpoints of the claimed weight and IgE ranges, would weigh 12.5 kg and have an IgE of 940 IU/mL. For such a representative subject, the calculated four week dosage is at least 188 mg ($0.016 \times 12.5 \times 940$), which would be increased to 225 mg every four weeks (the next 75 mg increment), and the calculated two week dosage is at least 94 mg ($188/2$), which would be increased to 150 mg every two weeks (the next 75 mg increment).

266. The two week dose of 150 mg is within the range of doses in alternative 2.

d) A POSA Would Have Been Motivated to Practice the Subject Matter of Alternative 1 and/or 2 of Claim 1 with a Reasonable Expectation of Success

267. A POSA would have been motivated to combine the teachings of *OUtMATCH-V26*, *Arasi*, and *PI2021* for at least the following reasons (Paragraphs 268-272).

268. *Arasi* teaches that there is a need for food allergy therapies. *Arasi* further teaches that among “the most promising therapeutic options,” omalizumab is the most used biologic (EX1006, 286) and that based on early stage clinical trials, it may be effective for food allergy (*id.* 287 (citing *Sampson* (EX1031), *Savage* (EX1032), and *Fiocchi 2019* (EX1029))).

269. Second, as noted in Paragraphs 232-244, 257, above, *OUtMATCH-V26* taught a study of omalizumab for the treatment of food allergies, and *Arasi* summarized the state of research on using omalizumab to treat food allergies, including discussion of the ongoing *OUtMATCH* study. A POSA therefore would have been motivated to combine these teachings regarding related subject matter.

270. Third, *Arasi* stated that the majority of studies of omalizumab report using a dose/frequency based on subject weight and total serum IgE, “according to asthma and nasal polyps indication,” which would have motivated a POSA to look to the omalizumab dosing regimen to treating asthma and polyps. *PI2021* provided Genentech’s dosing and administration regimens for asthma and nasal polyps at the time of invention. A POSA would have been motivated to combine these related teachings regarding the dosing of omalizumab and to use them with the teachings of *OUtMATCH-V26*, an omalizumab clinical trial in which Genetech is a collaborator. EX1005, 4.

271. A POSA would have had a reasonable expectation of success based on at least the following: (1) Omalizumab's known mechanism of action, IgE inhibition (*see* EX1038, 102); (2) OUtMATCH having received BTD (*see* EX1011, 1); (3) OUtMATCH having continued for over three years as of the May 2022 publication of *OUtMATCH-V26* (July 2019 – May 2022); (4) studies showing the safe and effective administration of omalizumab to subjects as young as two (*see* EX1017, 3); and (5) the many studies that demonstrated safe and effective administration of omalizumab for food allergy, as a monotherapy or in combination with OIT, including studies allowing 15 kg subjects and studies allowing baseline total serum IgE up to about 2000 IU/mL (*see* EX1008 (IgE $\leq$ 1172); EX1009; EX1018 (IgE $\leq$ about 1300; “no immediate local or systemic adverse reactions were documented, nor have any delayed reactions been reported”); EX1031; EX1032; EX1029.

* * *

272. For the above reasons, the combined teachings of *OUtMATCH-V26*, *Arasi*, and *PI2021* would have motivated a POSA to practice the subject matter of the first and/or second alternative of claim 1 with a reasonable expectation of success. Therefore, claim 1 would have been obvious to a POSA.

5. Claim 2

273. Claim 2 depends from claim 1 and recites three additional alternative dosing regimens, based on subject weight and total serum IgE level, which I refer to as alternatives 1, 2, and 3 of claim 2. Claim 2 additionally recites that “the total serum IgE level of the subject is determined prior to administration of a first dose of omalizumab.”

a) Dosing Regimen Alternatives 1, 2, and 3

274. The analysis that I applied in claim 1 with respect to the alternative dosing regimens applies equally to alternatives 1, 2, and 3 of claim 2. *See, e.g.*, Paragraphs 252-272.

- (1) **Alternative 1: “The method of claim 1, wherein the pharmaceutical composition is administered once about every two weeks and the dose of omalizumab is: 150 mg when the body weight of the subject is equal to or greater than 10 kg and less than or equal to 12 kg, and the total serum IgE level of the subject is greater than 600 IU/ml and less than or equal to 1500 IU/ml”**

275. A representative subject for alternative 1 of claim 2, determined by averaging the endpoints of the claimed weight and IgE ranges, would weigh 11 kg and have an IgE of 1050 IU/mL. For such a representative subject, the calculated four week dosage is at least 184.8 mg ($0.016 \times 11 \times 1050$), which would be increased to 225 mg every four weeks, and the calculated two week dosage is at least 92.4 mg ($184.8/2$), which would be increased to 150 mg every two weeks.

276. The two week dose of 150 mg is the same as the dose/frequency recited in alternative 1 of claim 2.

- (2) **Alternative 2: “The method of claim 1, wherein the pharmaceutical composition is administered once about every two weeks and the dose of omalizumab is: ... 150 mg when the body weight of the subject is greater than 12 kg and less than or equal to 15 kg, and the total serum IgE level of the subject is greater than 600 IU/ml and less than or equal to 1200 IU/ml”**

277. A representative subject for alternative 1 of claim 2, determined by averaging the endpoints of the claimed weight and IgE ranges, would weigh 13.5 kg and have an IgE of 900 IU/mL. For such a representative subject, the calculated four week dosage is at least 194.4 mg ($0.016 \times 13.5 \times 900$), which would be increased to 225 mg every four weeks, and the calculated two week dosage is 97.2 mg ($194.4/2$), which would be increased to 150 mg every two weeks.

278. The two week dose of 150 mg is the same as the dose/frequency recited in alternative 2 of claim 2.

- (3) **Alternative 3: “The method of claim 1, wherein the pharmaceutical composition is administered once about every two weeks and the dose of omalizumab is: ... 225 mg when the body weight of the subject is greater than 12 kg and less than or equal to 15 kg, and the total serum IgE level of the subject is greater than 1200 IU/ml and less than or equal to 1850 IU/ml”**

279. A representative subject for alternative 1 of claim 2, determined by averaging the endpoints of the claimed weight and IgE ranges, would weigh 13.5 kg and have an IgE of 1525 IU/mL. For such a representative subject, the calculated four week dosage is at least 329.4 mg ($0.016 \times 13.5 \times 1525$), which would be increased to 375 mg every four weeks, and the calculated two week dosage is at least 164.7 mg ($329.4/2$), which would be increased to 225 mg every two weeks.

280. The two week dose of 225 mg is the same as the dose/frequency recited in alternative 3 of claim 2.

b) “wherein the total serum IgE level of the subject is determined prior to administration of a first dose of omalizumab.”

281. *OUtMATCH-V26* teaches that the total serum IgE of the subject is determined before the first dose of omalizumab: “dose administered and the dosing interval are determined by serum total IgE level and body weight (measured before the start of treatment) per the study drug dosing table.” EX1005, 6.

282. *PI2021* also teaches, in the context of asthma, determining the total serum IgE of the subject before the first dose of omalizumab: “[d]etermine dose (mg) and dosing frequency by serum total IgE level (IU/mL) *measured before the start of treatment*, and body weight (kg).” EX1007, 1, 3, 4 (emphasis added).

283. In addition, *PI2021* taught that omalizumab increases total serum IgE (bound and unbound) because it forms an omalizumab-IgE complex that is eliminated from the body more slowly than free IgE: “Serum total IgE levels (i.e., bound and unbound) increased after the first dose due to the formation of omalizumab:IgE complexes, which have a slower elimination rate compared with free IgE.” EX1007, 22.

284. Accordingly, when administering omalizumab based on subject weight and serum IgE, a POSA would have been motivated to determine serum total IgE levels before starting treatment.

* * *

285. For the above reasons, and the reasons given with regard to claim 1 (see Paragraphs 245-272), the combined teachings of *OUtMATCH-V26*, *Arasi*, and *PI2021* would have motivated a POSA to practice the subject matter of alternatives 1, 2, or 3 of claim 2 with a reasonable expectation of success. Therefore, claim 2 would have been obvious to a POSA.

6. Claim 3

286. Claim 3 depends from claim 1 and recites an additional alternative dosing regimen, based on subject weight and total serum IgE level. Claim 3, like claim 2, additionally recites that “the total serum IgE level of the subject is determined prior to administration of a first dose of omalizumab.” The analysis

that I applied in claim 1 with respect to the alternative dosing regimens applies equally to claim 3. *See, e.g.,* Paragraphs 252-272.

- a) **“The method of claim 1, wherein the pharmaceutical composition is administered once about every four weeks and the dose of omalizumab is: 75 mg when the body weight of the subject is equal to or greater than 10 kg and less than or equal to 15 kg, and the total serum IgE level of the subject is equal to or greater than 30 IU/ml and less than or equal to 300 IU/ml”**

287. A representative subject for claim 3, determined by averaging the endpoints of the claimed weight and IgE ranges, would weigh 12.5 kg and have an IgE of 165 IU/mL. For such a representative subject, the calculated four week dosage is at least 33.0 mg ($0.016 \times 12.5 \times 165$), which would be increased to 75 mg every four weeks, and the calculated two week dosage is at least 16.5 mg ($33.0/2$), which would be increased to 75 mg every two weeks.

288. The four week dose of 75 mg is the same as the dose/frequency recited in claim 3.

- b) **“wherein the total serum IgE level of the subject is determined prior to administration of a first dose of omalizumab.”**

289. For the same reasons as explained in Paragraphs 281-285 when discussing this element in the context of claim 2, when administering omalizumab based on subject weight and serum IgE, a POSA would have been motivated to determine serum total IgE levels before starting treatment.

* * *

290. For the above reasons, and the reasons given with regard to claim 1 (see Paragraphs 245-272), the combined teachings of *OUtMATCH-V26*, *Arasi*, and *PI2021* would have motivated a POSA to practice the subject matter of claim 3 with a reasonable expectation of success. Therefore, claim 3 would have been obvious to a POSA.

7. Claim 4

291. Claim 4 depends from claim 1 and recites an additional alternative dosing regimen, based on subject weight and total serum IgE level. Claim 4, like claim 2, additionally recites that “the total serum IgE level of the subject is determined prior to administration of a first dose of omalizumab.” The analysis that I applied in claim 1 with respect to the alternative dosing regimens applies equally to claim 4. *See, e.g.*, Paragraphs 252-272.

- a) **“The method of claim 1, wherein the pharmaceutical composition is administered once about every four weeks and the dose of omalizumab is: 150 mg when the body weight of the subject is equal to or greater than 10 kg and less than or equal to 15 kg, and the total serum IgE level of the subject is greater than 300 IU/ml and less than or equal to 600 IU/ml”**

292. A representative subject for claim 4, determined by averaging the endpoints of the claimed weight and IgE ranges, would weigh 12.5 kg and have an IgE of 450 IU/mL. For such a representative subject, the calculated minimum four

week dosage is at least 90.0 mg ($0.016 \times 12.5 \times 450$), which would be increased to 150 mg every four weeks, and the calculated two week dosage is at least 45.0 mg ($90.0/2$), which would be increased to 75 mg every two weeks.

293. The four week dose of 150 mg is the same as the dose/frequency recited in claim 3.

b) “wherein the total serum IgE level of the subject is determined prior to administration of a first dose of omalizumab.”

294. For the same reasons as explained in Paragraphs 281-285 when discussing this element in the context of claim 2, when administering omalizumab based on subject weight and serum IgE, a POSA would have been motivated to determine serum total IgE levels before starting treatment.

* * *

295. For the above reasons, and the reasons given with regard to claim 1 (see Paragraphs 245-272), the combined teachings of *OUtMATCH-V26*, *Arasi*, and *PI2021* would have motivated a POSA to practice the subject matter of claim 4 with a reasonable expectation of success. Therefore, claim 4 would have been obvious to a POSA.

8. Claim 5

296. Claim 5 depends from claim 1 and recites four additional alternative dosing regimens, based on subject weight and total serum IgE level, which I refer

to as alternatives 1, 2, 3, and 4 of claim 5. Claim 5, like claim 2, additionally recites that “the total serum IgE level of the subject is determined prior to administration of a first dose of omalizumab.”

a) Dosing Regimen Alternatives 1, 2, 3, and 4

297. The analysis that I applied in claim 1 with respect to the alternative dosing regimens applies equally to alternatives 1, 2, 3, and 4 of claim 5. *See, e.g.*, Paragraphs 252-272.

- (1) Alternative 1: “The method of claim 1, wherein the pharmaceutical composition is administered to a subject having a body weight of greater than 12 kg and less than or equal to 15 kg at a dose of: 75 mg once about every four weeks if the total serum IgE level of the subject is equal to or greater than 30 IU/ml and less than or equal to 300 IU/ml”**

298. A representative subject for alternative 1 of claim 5, determined by averaging the endpoints of the claimed weight and IgE ranges, would weigh 13.5 kg and have an IgE of 165 IU/mL. For such a representative subject, the calculated four week dosage is at least 35.64 mg ($0.016 \times 13.5 \times 165$), which would be increased to 75 mg every four weeks, and the calculated two week dosage is 17.82 mg ($35.64/2$), which would be increased to 75 mg every two weeks.

299. The four week dose of 75 mg is the same as the dose/frequency recited in alternative 1 of claim 5.

- (2) **Alternative 2: “The method of claim 1, wherein the pharmaceutical composition is administered to a subject having a body weight of greater than 12 kg and less than or equal to 15 kg at a dose of: 150 mg once about every four weeks if the total serum IgE level of the subject is greater than 300 IU/ml and less than or equal to 600 IU/ml”**

300. A representative subject for alternative 2 of claim 5, determined by averaging the endpoints of the claimed weight and IgE ranges, would weigh 13.5 kg and have an IgE of 450 IU/mL. For such a representative subject, the calculated four week dosage is at least 97.2 mg ($0.016 \times 13.5 \times 450$), which would be increased to 150 mg every four weeks, and the calculated two week dosage is at least 48.6 mg ($97.2/2$), which would be increased to 75 mg every two weeks.

301. The four week dose of 150 mg is the same as the dose/frequency recited in alternative 2 of claim 2.

- (3) **Alternative 3: “The method of claim 1, wherein the pharmaceutical composition is administered to a subject having a body weight of greater than 12 kg and less than or equal to 15 kg at a dose of: 150 mg once about every two weeks if the total serum IgE level of the subject is greater than 600 IU/ml and less than or equal to 1200 IU/ml”**

302. A representative subject for alternative 3 of claim 5, determined by averaging the endpoints of the claimed weight and IgE ranges, would weigh 13.5 kg and have an IgE of 900 IU/mL. For such a representative subject, the

calculated four week dosage is at least 194.4 mg ($0.016 \times 13.5 \times 900$), which would be increased to 225 mg every four weeks, and the calculated two week dosage is at least 97.2 mg ($194.4/2$), which would be increased to 150 mg every two weeks.

303. The two week dose of 150 mg is the same as the dose recited in alternative 3 of claim 2.

- (4) Alternative 4: “The method of claim 1, wherein the pharmaceutical composition is administered to a subject having a body weight of greater than 12 kg and less than or equal to 15 kg at a dose of: 225 mg once about every two weeks if the total serum IgE level of the subject is greater than 1200 IU/ml and less than or equal to 1850 IU/ml”**

304. A representative subject for alternative 4 of claim 5, determined by averaging the endpoints of the claimed weight and IgE ranges, would weigh 13.5 kg and have an IgE of 1525 IU/mL. For such a representative subject, the calculated four week dosage is at least 329.4 mg ($0.016 \times 13.5 \times 1525$), which would be increased to 375 mg every four weeks, and the calculated two week dosage is at least 164.7 mg ($329.4/2$), which would be increased to 225 mg every two weeks.

305. The two week dose of 225 mg is the same as the dose recited in alternative 4 of claim 2.

b) “wherein the total serum IgE level of the subject is determined prior to administration of a first dose of omalizumab.”

306. For the same reasons as explained in Paragraphs 281-285 when discussing this element in the context of claim 2, when administering omalizumab based on subject weight and serum IgE, a POSA would have been motivated to determine serum total IgE levels before starting treatment.

* * *

307. For the above reasons, and the reasons given with regard to claim 1 (see Paragraphs 245-272), the combined teachings of *OUtMATCH-V26*, *Arasi*, and *PI2021* would have motivated a POSA to practice the subject matter of claim 5 with a reasonable expectation of success. Therefore, claim 5 would have been obvious to a POSA.

9. Claim 10

308. Claim 10 depends from claim 1 and recites two additional alternative dosing regimens, based on subject weight and total serum IgE level, which I refer to as alternatives 1 and 2 of claim 10. Claim 10, like claim 2, additionally recites that “the total serum IgE level of the subject is determined prior to administration of a first dose of omalizumab.”

a) Dosing Regimen Alternatives 1 and 2

309. The analysis that I applied in claim 1 with respect to the alternative dosing regimens applies equally to alternatives 1 and 2 of claim 10. *See, e.g.*, Paragraphs 252-272.

- (1) Alternative 1: “The method of claim 1, wherein the pharmaceutical composition is administered about once every two weeks and the dose of omalizumab is: 150 mg when the body weight of the subject is equal to or greater than 10 kg and less than or equal to 15 kg, and the total serum IgE level of the subject is greater than 600 IU/ml and less than or equal to 1200 IU/ml”**

310. A representative subject for alternative 1 of claim 10, determined by averaging the endpoints of the claimed weight and IgE ranges, would weigh 12.5 kg and have an IgE of 900 IU/mL. For such a representative subject, the calculated four week dosage is at least 180.0 mg ($0.016 \times 12.5 \times 900$), which would be increased to 225 mg every four weeks, and the calculated two week dosage is at least 90.0 mg ($180.0/2$), which would be increased to 150 mg every two weeks.

311. The two week dose of 150 mg is the same as the dose/frequency recited in alternative 1 of claim 10.

- (2) Alternative 2: “The method of claim 1, wherein the pharmaceutical composition is administered about once every two weeks and the dose of omalizumab is: 150 mg when the body weight of the subject is equal to or greater than 10 kg and less than or equal to 12 kg, and the total serum**

**IgE level of the subject is greater than 1200
IU/ml and less than or equal to 1500 IU/ml”**

312. A representative subject for alternative 2 of claim 10, determined by averaging the endpoints of the claimed weight and IgE ranges, would weigh 11 kg and have an IgE of 1350 IU/mL. For such a representative subject, the calculated four week dosage is at least 237.6 mg ($0.016 \times 11 \times 1350$), which would be increased to 300 mg every four weeks, and the calculated two week dosage is at least 118.8 mg ($237.6/2$), which would be increased to 150 mg every two weeks.

313. The two week dose of 150 mg is the same as the dose/frequency recited in alternative 2 of claim 10.

**b) “wherein the total serum IgE level of the subject is
determined prior to administration of a first dose of
omalizumab.”**

314. For the same reasons as explained in Paragraphs 281-285 when discussing this element in the context of claim 2, when administering omalizumab based on subject weight and serum IgE, a POSA would have been motivated to determine serum total IgE levels before starting treatment.

* * *

315. For the above reasons, and the reasons given with regard to claim 1 (see Paragraphs 245-272), the combined teachings of *OUtMATCH-V26*, *Arasi*, and *PI2021* would have motivated a POSA to practice the subject matter of claim 10

with a reasonable expectation of success. Therefore, claim 10 would have been obvious to a POSA.

10. Claim 11

316. Claim 11 depends from claim 1 and recites two additional alternative dosing regimens, based on subject weight and total serum IgE level, which I refer to as alternatives 1 and 2 of claim 11. Claim 11, like claim 2, additionally recites that “the total serum IgE level of the subject is determined prior to administration of a first dose of omalizumab.”

a) Dosing Regimen Alternatives 1 and 2

317. The analysis that I applied in claim 1 with respect to the alternative dosing regimens applies equally to alternatives 1 and 2 of claim 11. *See, e.g.*, Paragraphs 252-272.

- (1) Alternative 1: “The method of claim 1, wherein the pharmaceutical composition is administered about once every four weeks and the dose of omalizumab is: 75 mg when the body weight of the subject is equal to or greater than 10 kg and less than or equal to 15 kg, and the total serum IgE level of the subject is equal to or greater than 30 IU/ml and less than or equal to 300 IU/ml”**

318. A representative subject for alternative 1 of claim 11, determined by averaging the endpoints of the claimed weight and IgE ranges, would weigh 12.5 kg and have an IgE of 165 IU/mL. For such a representative subject, the calculated

four week dosage is at least 33.0 mg ($0.016 \times 12.5 \times 165$), which would be increased to 75 mg every four weeks, and the calculated two week dosage is at least 16.5 mg ($33.0/2$), which would be increased to 75 mg every two weeks.

319. The four week dose of 75 mg is the same as the dose/frequency recited in alternative 1 of claim 11.

(2) Alternative 2: “The method of claim 1, wherein the pharmaceutical composition is administered about once every four weeks and the dose of omalizumab is: 150 mg when the body weight of the subject is equal to or greater than 10 kg and less than or equal to 15 kg, and the total serum IgE level of the subject is greater than 300 IU/ml and less than or equal to 600 IU/ml”

320. A representative subject for alternative 2 of claim 11, determined by averaging the endpoints of the claimed weight and IgE ranges, would weigh 12.5 kg and have an IgE of 450 IU/mL. For such a representative subject, the calculated four week dosage is at least 90.0 mg ($0.016 \times 12.5 \times 450$), which would be increased to 150 mg every four weeks, and the calculated two week dosage is at least 45.0 mg ($90.0/2$), which would be increased to 75 mg every two weeks.

321. The four week dose of 150 mg is the same as the dose/frequency recited in alternative 2 of claim 11.

b) “wherein the total serum IgE level of the subject is determined prior to administration of a first dose of omalizumab.”

322. For the same reasons as explained in Paragraphs 281-285 when discussing this element in the context of claim 2, when administering omalizumab based on subject weight and serum IgE, a POSA would have been motivated to determine serum total IgE levels before starting treatment.

* * *

323. For the above reasons, and the reasons given with regard to claim 1 (see Paragraphs 245-272), the combined teachings of *OUtMATCH-V26*, *Arasi*, and *PI2021* would have motivated a POSA to practice the subject matter of claim 11 with a reasonable expectation of success. Therefore, claim 11 would have been obvious to a POSA.

11. Claim 12

324. Claim 12 claims a method of treating a human subject having an allergy to a food allergen, wherein the dosing amount and frequency are based on subject weight and IgE level determined prior to the first dose of omalizumab. Four dose/frequency alternatives are recited, which I refer to as alternatives 1, 2, 3, and 4 of claim 12.

- a) **“A method of treating a human subject having an allergy to a food allergen, the method comprising: (i) administering to the subject by subcutaneous injection ... a pharmaceutical composition comprising a dose of omalizumab”**

325. As explained in Paragraphs 247-251, above, with respect to the same element in claim 1, it would have been obvious to a POSA to administer omalizumab subcutaneously for the treatment of food allergies.

b) Dosing Regimen Alternatives 1, 2, 3, and 4

326. The analysis that I applied in claim 1 with respect to the alternative dosing regimens applies equally to alternatives 1, 2, 3, and 4 of claim 12. *See, e.g.*, Paragraphs 252-272.

- (1) **Alternative 1: “administering to the subject ... once about every four weeks a pharmaceutical composition comprising a dose of omalizumab of: 150 mg when body weight of the subject is equal to or greater than 10 kg and less than or equal to 15 kg, and total serum IgE level of the subject is greater than 300 IU/ml and less than or equal to 600 IU/ml”**

327. A representative subject for alternative 1 of claim 12, determined by averaging the endpoints of the claimed weight and IgE ranges, would weigh 12.5 kg and have an IgE of 450 IU/mL. For such a representative subject, the calculated four week dosage is at least 90.0 mg ($0.016 \times 12.5 \times 450$), which would be increased to 150 mg every four weeks, and the calculated two week dosage is at least 45.0 mg ($90.0/2$), which would be increased to 75 mg every two weeks.

328. The four week dose of 150 mg is the same as the dose/frequency recited in alternative 1 of claim 12.

- (2) **Alternative 2: “administering to the subject ... once about every two weeks a pharmaceutical composition comprising a dose of omalizumab of: 150 mg when body weight of the subject is equal to or greater than 10 kg and less than or equal to 12 kg, and total serum IgE level of the subject is greater than 600 IU/ml and less than or equal to 1500 IU/ml”**

329. A representative subject for alternative 2 of claim 12, determined by averaging the endpoints of the claimed weight and IgE ranges, would weigh 11 kg and have an IgE of 1050 IU/mL. For such a representative subject, the calculated four week dosage is at least 184.8 mg ($0.016 \times 11 \times 1050$), which would be increased to 225 mg every four weeks, and the calculated two week dosage is at least 92.4 mg ($184.8/2$), which would be increased to 150 mg every two weeks.

330. The two week dose of 150 mg is the same as the dose/frequency recited in alternative 2 of claim 12.

- (3) **Alternative 3: “administering to the subject ... once about every two weeks a pharmaceutical composition comprising a dose of omalizumab of: 150 mg when body weight of the subject is greater than 12 kg and less than or equal to 15 kg, and total serum IgE level of the subject is greater than 600 IU/ml and less than or equal to 1200 IU/ml**

331. A representative subject for alternative 3 of claim 12, determined by averaging the endpoints of the claimed weight and IgE ranges, would weigh 13.5 kg and have an IgE of 900 IU/mL. For such a representative subject, the calculated four week dosage is at least 194.4 mg ($0.016 \times 13.5 \times 900$), which would be increased to 225 mg every four weeks, and the calculated two week dosage is at least 97.2 mg ($194.4/2$), which would be increased to 150 mg every two weeks.

332. The two week dose of 150 mg is the same as the dose recited in alternative 3 of claim 12.

- (4) Alternative 4: “administering to the subject ... once about every two weeks a pharmaceutical composition comprising a dose of omalizumab of: 225 mg when body weight of the subject is greater than 12 kg and less than or equal to 15 kg, and total serum IgE level of the subject is greater than 1200 IU/ml and less than or equal to 1850 IU/ml”**

333. A representative subject for alternative 4 of claim 12, determined by averaging the endpoints of the claimed weight and IgE ranges, would weigh 13.5 kg and have an IgE of 1525 IU/mL. For such a representative subject, the calculated four week dosage is at least 329.4 mg ($0.016 \times 13.5 \times 1525$), which would be increased to 375 mg every four weeks, and the calculated two week dosage is at least 164.7 mg ($329.4/2$), which would be increased to 225 mg every two weeks.

334. The two week dose of 225 mg is the same as the dose recited in alternative 4 of claim 12.

- c) **“wherein the total serum IgE level of the subject is determined prior to administration of a first dose of omalizumab.”**

335. For the same reasons as explained in Paragraphs 281-285 when discussing this element in the context of claim 2, when administering omalizumab based on subject weight and serum IgE, a POSA would have been motivated to determine serum total IgE levels before starting treatment.

* * *

336. For the above reasons, the combined teachings of *OUtMATCH-V26*, *Arasi*, and *PI2021* would have motivated a POSA to practice the subject matter of claim 12 with a reasonable expectation of success. Therefore, claim 12 would have been obvious to a POSA.

12. Claim 17

337. Claim 17 claims a method of treating a human subject having an allergy to a food allergen, wherein the dosing amount and frequency are based on subject weight and IgE level determined prior to the first dose of omalizumab. Five dose/frequency alternatives are recited, which I refer to as alternatives 1, 2, 3, 4, and 5 of claim 17.

- a) **“A method of treating a human subject having an allergy to a food allergen, the method comprising:**

(i) administering to the subject by subcutaneous injection ... a pharmaceutical composition comprising a dose of omalizumab”

338. As explained in Paragraphs 247-251, above, with respect to the same element in claim 1, it would have been obvious to a POSA to administer omalizumab subcutaneously for the treatment of food allergies.

b) Dosing Regimen Alternatives 1, 2, 3, 4, and 5

339. The analysis that I applied in claim 1 with respect to the alternative dosing regimens applies equally to alternatives 1, 2, 3, 4, and 5 of claim 17. *See, e.g.,* Paragraphs 252-272.

(1) Alternative 1: “administering to the subject ... once about every four weeks a pharmaceutical composition comprising a dose of omalizumab of: 75 mg when body weight of the subject is equal to or greater than 10 kg and less than or equal to 15 kg, and total serum IgE level of the subject is equal to or greater than 30 IU/ml and less than or equal to 300 IU/ml”

340. A representative subject for alternative 1 of claim 17, determined by averaging the endpoints of the claimed weight and IgE ranges, would weigh 12.5 kg and have an IgE of 165 IU/mL. For such a representative subject, the calculated four week dosage is at least 33.0 mg ($0.016 \times 12.5 \times 165$), which would be increased to 75 mg every four weeks, and the calculated two week dosage is at least 16.5 mg ($33.0/2$), which would be increased to 75 mg every two weeks.

341. The four week dose of 75 mg is the same as the dose/frequency recited in alternative 1 of claim 17.

- (2) **Alternative 2: “administering to the subject ... once about every four weeks a pharmaceutical composition comprising a dose of omalizumab of: 150 mg when body weight of the subject is equal to or greater than 10 kg and less than or equal to 15 kg, and total serum IgE level of the subject is greater than 300 IU/ml and less than or equal to 600 IU/ml”**

342. A representative subject for alternative 2 of claim 17, determined by averaging the endpoints of the claimed weight and IgE ranges, would weigh 12.5 kg and have an IgE of 450 IU/mL. For such a representative subject, the calculated four week dosage is at least 90.0 mg ($0.016 \times 12.5 \times 450$), which would be increased to 150 mg every four weeks, and the calculated two week dosage is at least 45.0 mg ($90.0/2$), which would be increased to 75 mg every two weeks.

343. The four week dose of 150 mg is the same as the dose/frequency recited in alternative 2 of claim 17.

- (3) **Alternative 3: “administering to the subject ... once about every two weeks a pharmaceutical composition comprising a dose of omalizumab of: 150 mg when body weight of the subject is equal to or greater than 10 kg and less than or equal to 12 kg, and total serum IgE level of the subject is greater than 600 IU/ml and less than or equal to 1500 IU/ml”**

344. A representative subject for alternative 3 of claim 17, determined by averaging the endpoints of the claimed weight and IgE ranges, would weigh 11 kg and have an IgE of 1050 IU/mL. For such a representative subject, the calculated four week dosage is at least 184.8 mg ($0.016 \times 11 \times 1050$), which would be increased to 225 mg every four weeks, and the calculated two week dosage is at least 92.4 mg ($184.8/2$), which would be increased to 150 mg every two weeks.

345. The two week dose of 150 mg is the same as the dose/frequency recited in alternative 3 of claim 17.

(4) Alternative 4: “administering to the subject ... once about every two weeks a pharmaceutical composition comprising a dose of omalizumab of: 150 mg when body weight of the subject is greater than 12 kg and less than or equal to 15 kg, and total serum IgE level of the subject is greater than 600 IU/ml and less than or equal to 1200 IU/ml

346. A representative subject for alternative 4 of claim 17, determined by averaging the endpoints of the claimed weight and IgE ranges, would weigh 13.5 kg and have an IgE of 900 IU/mL. For such a representative subject, the calculated four week dosage is at least 194.4 mg ($0.016 \times 13.5 \times 900$), which would be increased to 225 mg every four weeks, and the calculated two week dosage is at least 97.2 mg ($194.4/2$), which would be increased to 150 mg every two weeks.

347. The two week dose of 150 mg is the same as the dose recited in alternative 4 of claim 17.

- (5) **Alternative 5: “administering to the subject ... once about every two weeks a pharmaceutical composition comprising a dose of omalizumab of: 225 mg when body weight of the subject is greater than 12 kg and less than or equal to 15 kg, and total serum IgE level of the subject is greater than 1200 IU/ml and less than or equal to 1850 IU/ml”**

348. A representative subject for alternative 5 of claim 17, determined by averaging the endpoints of the claimed weight and IgE ranges, would weigh 13.5 kg and have an IgE of 1525 IU/mL. For such a representative subject, the calculated four week dosage is at least 329.4 mg ($0.016 \times 13.5 \times 1525$), which would be increased to 375 mg every four weeks, and the calculated two week dosage is at least 164.7 mg ($329.4/2$), which would be increased to 225 mg every two weeks.

349. The two week dose of 225 mg is the same as the dose recited in alternative 5 of claim 17.

- c) **“wherein the total serum IgE level of the subject is determined prior to administration of a first dose of omalizumab.”**

350. For the same reasons as explained in Paragraphs 281-285 when discussing this element in the context of claim 2, when administering omalizumab

based on subject weight and serum IgE, a POSA would have been motivated to determine serum total IgE levels before starting treatment.

* * *

351. For the above reasons, the combined teachings of *OUtMATCH-V26*, *Arasi*, and *PI2021* would have motivated a POSA to practice the subject matter of claim 17 with a reasonable expectation of success. Therefore, claim 17 would have been obvious to a POSA.

13. Claim 25

352. Claim 25 claims a method of treating a human subject having an allergy to a food allergen, wherein the dosing amount and frequency are based on subject weight and IgE level determined prior to the first dose of omalizumab. Three dose/frequency alternatives are recited, which I refer to as alternatives 1, 2, and 3 of claim 25.

- a) “A method of treating a human subject having an allergy to a food allergen, the method comprising: administering to the subject ... by subcutaneous injection a pharmaceutical composition comprising a dose of omalizumab”**

353. As explained in Paragraphs 247-251, above, with respect to the same element in claim 1, it would have been obvious to a POSA to administer omalizumab subcutaneously for the treatment of food allergies.

b) Dosing Regimen Alternatives 1, 2, and 3

354. The analysis that I applied in claim 1 with respect to the alternative dosing regimens applies equally to alternatives 1, 2, and 3 of claim 25. *See, e.g.*, Paragraphs 252-272.

- (1) Alternative 1: “administering to the subject having a body weight equal to or greater than 10 kg and less than or equal to 12 kg ... a pharmaceutical composition comprising a dose of omalizumab of: 75 mg once about every four weeks if total serum IgE level of the subject is equal to or greater than 30 IU/ml and less than or equal to 300 IU/ml”**

355. A representative subject for alternative 1 of claim 25, determined by averaging the endpoints of the claimed weight and IgE ranges, would weigh 11 kg and have an IgE of 165 IU/mL. For such a representative subject, the calculated four week dosage is at least 29.04 mg ($0.016 \times 11 \times 165$), which would be increased to 75 mg every four weeks, and the calculated two week dosage is at least 14.52 mg ($29.04/2$), which would be increased to 75 mg every two weeks.

356. The four week dose of 75 mg is the same as the dose/frequency recited in alternative 1 of claim 25.

- (2) Alternative 2: “administering to the subject having a body weight equal to or greater than 10 kg and less than or equal to 12 kg ... a pharmaceutical composition comprising a dose of omalizumab of: 150 mg once about every four weeks if total serum IgE level of the**

subject is greater than 300 IU/ml and less than or equal to 600 IU/ml”

357. A representative subject for alternative 2 of claim 25, determined by averaging the endpoints of the claimed weight and IgE ranges, would weigh 11 kg and have an IgE of 450 IU/mL. For such a representative subject, the calculated four week dosage is at least 79.2 mg ($0.016 \times 11 \times 450$), which would be increased to 150 mg every four weeks, and the calculated two week dosage is at least 39.6 mg ($79.2/2$), which would be increased to 75 mg every two weeks.

358. The four week dose of 150 mg is the same as the dose/frequency recited in alternative 2 of claim 25.

(3) Alternative 3: “administering to the subject having a body weight equal to or greater than 10 kg and less than or equal to 12 kg ... a pharmaceutical composition comprising a dose of omalizumab of: 150 mg once about every two weeks if total serum IgE level of the subject is greater than 600 IU/ml and less than or equal to 1500 IU/ml”

359. A representative subject for alternative 3 of claim 25, determined by averaging the endpoints of the claimed weight and IgE ranges, would weigh 11 kg and have an IgE of 1050 IU/mL. For such a representative subject, the calculated four week dosage is at least 184.8 mg ($0.016 \times 11 \times 1050$), which would be increased to 225 mg every four weeks, and the calculated two week dosage is at least 92.4 mg ($184.8/2$), which would be increased to 150 mg every two weeks.

360. The two week dose of 150 mg is the same as the dose/frequency recited in alternative 3 of claim 25.

- c) **“wherein the total serum IgE level of the subject is determined prior to administration of a first dose of omalizumab.”**

361. For the same reasons as explained in Paragraphs 281-285 when discussing this element in the context of claim 2, when administering omalizumab based on subject weight and serum IgE, a POSA would have been motivated to determine serum total IgE levels before starting treatment.

* * *

362. For the above reasons, the combined teachings of *OUtMATCH-V26*, *Arasi*, and *PI2021* would have motivated a POSA to practice the subject matter of claim 25 with a reasonable expectation of success. Therefore, claim 25 would have been obvious to a POSA.

14. Claims 6, 13, 18, and 26

363. Claims 6, 13, 18, and 26 depend from claims 2, 12, 17, and 25, respectively, and further require that the body weight of the subject is determined prior to administration of a first dose of omalizumab.

364. As explained above, a POSA would have been motivated to administer at least 0.016 mg omalizumab per kg of subject body weight per IU/mL of baseline serum IgE. A POSA would have understood that to use subject's body

weight to determine the amount to administer in the first dose would require determining the subject's body weight prior to administering the first dose.

365. Based on the combined teachings of *Arasi* and *OUtMATCH-V26*, a POSA would have been motivated to determine the body weight of the subject prior to administration of omalizumab with a reasonable expectation of success.

366. For these reasons and the reasons set forth with respect to claims 2, 12, 17, and 25 (*see* Paragraphs 273-285, 324-362), a POSA would have been motivated to practice the subject matter of claims 6, 13, 18, and 26 with a reasonable expectation of success. Therefore, the combined disclosures of *OUtMATCH-V26*, *Arasi*, and *PI2021* would have rendered claims 6, 13, 18, and 26 obvious to a POSA.

15. Claims 7, 16, 19, and 29

367. Claims 7, 16, 19, and 29 depend from claims 2, 12, 17, and 25, respectively, and further require that the subject is not receiving concurrent oral immunotherapy with the food allergen.

368. *Arasi* is titled “Omalizumab as monotherapy for food allergy” and discloses several studies that “support[] the use of Omalizumab as monotherapy in food allergy.” EX1006, 288. The monotherapy studies discussed in *Arasi* include *Fiocchi 2019* (EX1029), a 2019 retrospective observational study of 15 pediatric patients. Regarding *Fiocchi 2019*, *Arasi* states that “[a]fter 4 months of

Omalizumab treatment, all patients experienced an increase in their eliciting threshold to each food tested,” that 11 patients “asymptotically consumed the full challenge amount,” and that the results “represent[ed] a statistically significant improvement for egg, milk, baked milk, and wheat.” EX1006, 288.

369. In addition, *OUtMATCH-V26* included an omalizumab monotherapy arm. EX1005, 6; EX1006, 289.

370. Based on the combined teachings of *Arasi* and *OUtMATCH-V26*, a POSA would have been motivated to use omalizumab as a monotherapy to treat food allergy with a reasonable expectation of success.

371. For these reasons and the reasons set forth with respect to claims 2, 12, 17, and 25 (*see* Paragraphs 273-285, 324-362), a POSA would have been motivated to practice the subject matter of claims 7, 16, 19, and 29 with a reasonable expectation of success. Therefore, the combined disclosures of *OUtMATCH-V26*, *Arasi*, and *PI2021* would have rendered claims 7, 16, 19, and 29 obvious to a POSA.

16. Claims 8, 15, 22, 23, and 28

372. Claim 22 depends from claim 17 and further requires that the treating comprises reducing an allergic reaction following exposure of the subject to the food allergen. A POSA would have understood that such exposure would include accidental exposure. Claims 8, 15, 23, and 28 depend from claims 2, 12, 22, and

25, respectively, and further require that the treating comprises reducing an allergic reaction following accidental exposure of the subject to the food allergen.

373. Based on the teachings in *OUtMATCH-V26* and the studies described in *Arasi*, a POSA would have reasonably expected that treatment with omalizumab, wherein the dose and frequency are determined as explained above, would reduce an allergic reaction following accidental exposure of a subject to a food allergen.

374. For these reasons and the reasons set forth with respect to claims 2, 12, 17, and 25 (*see* Paragraphs 273-285, 324-362), a POSA would have been motivated to practice the subject matter of claims 8, 15, 22, 23, and 28 with a reasonable expectation of success. Therefore, the combined disclosures of *OUtMATCH-V26*, *Arasi*, and *PI2021* would have rendered claims 8, 15, 22, 23, and 28 obvious to a POSA.

17. Claims 9, 14, 24, and 27

375. Claims 9, 14, 24, and 27 depend from claims 2, 12, 22, and 25, respectively, and further require that the treating comprises reducing a moderate-to-severe allergic reaction following exposure of the subject to the food allergen.

376. Based on the teachings of *OUtMATCH-V26* and the studies described in *Arasi*, a POSA would have reasonably expected that treatment with omalizumab, wherein the dose and frequency are determined as explained above,

would reduce a moderate-to-severe allergic reaction following exposure of a subject to a food allergen.

377. For these reasons and the reasons set forth with respect to claims 2, 12, 17, and 25 (*see* Paragraphs 273-285, 324-362), a POSA would have been motivated to practice the subject matter of claims 9, 14, 24, and 27 with a reasonable expectation of success. Therefore, the combined disclosures of *OUtMATCH-V26*, *Arasi*, and *PI2021* would have rendered claims 9, 14, 24, and 27 obvious to a POSA.

18. Claim 20

378. Claim 20 depends from claim 17 and further requires that the subject is from one year to five years of age.

379. As explained above, a POSA would have been motivated to use omalizumab to treat subjects one to five years of age because food allergy was known to impact 1-10% of infants and pre-school aged children and was known to be the main etiology of anaphylaxis in children. EX1006; EX1030, 1007.

380. Moreover, the *OUtMATCH-V26* study was designed to include subjects as “1 to less than 56 years of age,” which encompasses subjects from one to five years of age. EX1005, 5.

381. In view of the combined teachings of *OUtMATCH-V26* and *Arasi*, a POSA would have been motivated to use omalizumab to treat infants and pre-

school aged children, which would include subjects from one year to five years of age, with a reasonable expectation of success. *See* EX1005, 5; EX1030, 1007.

382. For these reasons and the reasons set forth with respect to claim 17 (*see* Paragraphs 337-351), a POSA would have been motivated to practice the subject matter of claim 20 with a reasonable expectation of success. Therefore, the combined disclosures of *OUtMATCH-V26*, *Arasi*, and *PI2021* would have rendered claim 20 obvious to a POSA.

19. Claim 21

383. Claim 21 depends from claim 17 and further requires that the subject has an allergy to peanut and to one or more of milk, egg, and cashew.

384. *OUtMATCH-V26* states that it is a study of subjects “allergic to peanut and at least two other foods (including milk, egg, wheat, cashew, hazelnut, or walnut).” EX1005, 5. *Arasi* describes omalizumab monotherapy studies in subjects having peanut allergies (*Sampson*) and in subjects having, amongst others, milk and egg allergies (*Fiocchi 2019*), and describes each of those studies as observing reduced allergic responses in the subjects after administration of omalizumab. EX1006, 288.

385. For these reasons and the reasons set forth with respect to claim 17 (*see* Paragraphs 337-351), a POSA would have been motivated to practice the subject matter of claim 21 with a reasonable expectation of success. Therefore, the

combined disclosures of *OUtMATCH-V26*, *Arasi*, and *PI2021* would have rendered claim 21 obvious to a POSA.

F. Objective Indicia of Non-Obviousness

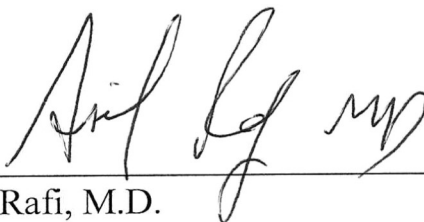
386. I am not aware of any relevant “objective indicia” of non-obviousness that would relate to the particular elements of claims 1-29 of *US959*. I may respond in the future to any objective indicia of which I become aware.

VIII. CONCLUDING STATEMENTS

387. In signing this declaration, I understand that the declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I acknowledge that I may be subject to cross-examination in this case and that cross-examination will take place within the United States. If cross-examination is required of me, I will appear for cross-examination within the United States during the time allotted for cross-examination.

388. I declare that all statements made herein of my knowledge are true, and that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: 5/22/2020



Asif Rafi, M.D.

APPENDIX – LIST OF EXHIBITS RELIED UPON

In preparing my declaration, I relied upon the exhibits cited below, and any other document cited in my declaration.

Exhibit No.	Description
1001	U.S. Patent No. 12,030,959 to Owen et al. (July 9, 2024) (“US959”)
1002	Declaration of Dr. Asif Rafi in Support of Petition for Inter Partes Review of U.S. Patent No. 12,030,959
1003	<i>Curriculum Vitae</i> of Dr. Asif Rafi
1004	Excerpts of prosecution history of U.S. Application No. 18/486,053, now U.S. Patent No. 12,030,959
1005	NCT03881696, <i>Omalizumab as Monotherapy and as Adjunct Therapy to Multi-Allergen OIT in Food Allergic Participants</i> , U.S. NATIONAL LIBRARY OF MEDICINE, CLINICALTRIALS.GOV (Version 26, May 2, 2022), https://clinicaltrials.gov/study/NCT03881696?tab=history&a=26#version-content-panel (“OUtMATCH-V26”)
1006	Stefanie Arasi et al., <i>Omalizumab as monotherapy for food allergy</i> , 21 CURR. OPIN. ALLERGY CLIN. IMMUNOL. 286-291 (June 2021) (“Arasi”)
1007	<i>XOLAIR® Prescribing Information</i> , FOOD AND DRUG ADMINISTRATION (July 2021), https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/103976s5239lbl.pdf (“PI2021”)
1008	Andrew J. MacGinnitie et al., <i>Omalizumab facilitates rapid oral desensitization for peanut allergy</i> , 139 J. ALLERGY CLIN. IMMUNOL. 873-881.e8 (2016) (“MacGinnitie”)
1009	Phillipe Bégin et al., <i>Phase I results of safety and tolerability in a rush oral immunotherapy protocol to multiple foods using Omalizumab</i> , 10:7 ALLERGY ASTHMA & CLIN. IMMUNOL. 1-10s.3 (2014) (“Bégin”)
1010	Abstract for Maurizio Mennini et al., <i>Omalizumab gets tolerance in patients with severe food allergy</i> , in <i>Meeting Abstracts, Proceedings of the 2017 WAO Symposium on Hot Topics in Allergy: Pediatric & Regulatory Aspects</i> , WORLD ALLERGY ORG. J. 10(Suppl. 2):39, page 15 (A42) (Nov. 16, 2017) (“Mennini”)

Exhibit No.	Description
1011	<i>FDA Grants Breakthrough Therapy Designation for Xolair (Omalizumab) for Food Allergies</i> , GENETECH: PRESS RELEASES (Aug. 12, 2018) (“ <i>BTD-PR</i> ”), https://www.gene.com/media/press-releases/14740/2018-08-12/fda-grants-breakthrough-therapy-designat
1012	<i>Breakthrough Therapy</i> , FOOD AND DRUG ADMINISTRATION (Jan. 4, 2018), available at https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/breakthrough-therapy (“ <i>BTD-FDA</i> ”)
1013	<i>Birth to 24 months: Boys Length-for-age and Weight-for-age percentiles</i> , CENTERS FOR DISEASE CONTROL AND PREVENTION (Nov. 1, 2009), available at https://www.cdc.gov/growthcharts/data/who/GrChrt_Boys_24LW_100611.pdf (“ <i>≤2 Boys</i> ”)
1014	<i>2 to 20 years: Boys Stature-for-age and Weight for age percentiles</i> , CENTERS FOR DISEASE CONTROL AND PREVENTION, (Nov. 21, 2000), available at https://www.cdc.gov/growthcharts/data/set1clinical/cj41c021.pdf (“ <i>≥2 Boys</i> ”)
1015	<i>Birth to 24 months: Girls Length-for-age and Weight-for-age percentiles</i> , CENTERS FOR DISEASE CONTROL AND PREVENTION (Nov. 1, 2009), available at https://www.cdc.gov/growthcharts/data/who/GrChrt_Girls_24LW_9210.pdf (“ <i>≤2 Girls</i> ”)
1016	<i>2 to 20 years: Girls Stature-for-age and Weight for age percentiles</i> , CENTERS FOR DISEASE CONTROL AND PREVENTION, (Nov. 21, 2000), available at https://www.cdc.gov/growthcharts/data/set1clinical/cj41c022.pdf (“ <i>≥2 Girls</i> ”)
1017	Wanda Phipatanakul et al., <i>Preventing Asthma in High Risk Kids (PARK) with Omalizumab: Design, Rationale, Methods, Lessons Learned and Adaptation</i> , 100 CONTEMP. CLIN. TRIALS 106228 (Jan. 2021) (“ <i>Phipatanakul</i> ”)
1018	Judit Crespo et al., <i>Real life study of the use of omalizumab for pediatric patients with multiple food allergies</i> , 49 ALLERGOL IMMUNOPATHOL (MADR) 2:15-22 (2021) (“ <i>Crespo</i> ”)
1019	<i>XOLAIR® Prescribing Information</i> , FOOD AND DRUG ADMINISTRATION (March 2014) (“ <i>PI2014</i> ”)

Exhibit No.	Description
1020	Abstract for Stefanie Arasi et al., <i>Omalizumab Gets Tolerance In Patients With Severe Food Allergy: A Real-Live Study</i> , 143 J. ALLERGY CLIN. IMMUNOL. 2 (Feb. 2019) (“ <i>Arasi Abstract</i> ”)
1021	<i>Clinical trial to evaluate experimental treatment in people allergic to multiple foods</i> , NATIONAL INSTITUTES OF HEALTH (Aug. 1, 2019) (“ <i>NIH-PR</i> ”)
1022	Sandra Andorf et al., <i>Anti-IgE Treatment with Oral Immunotherapy in Multifood Allergic Participants: Results of a Randomized, Double-blinded Control Trial</i> , 3 LANCET GASTROENTEROL HEPATOL., 2:85-94 (Feb. 2018) (“ <i>Andorf 2018</i> ”)
1023	Asif Rafi et al., <i>Effects of omalizumab in patients with food allergy</i> , 31 ALLERGY AND ASTHMA PROC. 76-83 (2010) (“ <i>Rafi</i> ”)
1024	Pena Peloché et al., <i>Severe food allergy in children. Omalizumab as an alternative treatment to elimination diet</i> , CLINICAL AND TRANSLATIONAL ALLERGY, 1(Suppl 1):P55 (Feb. 2011) (“ <i>Peloché Poster</i> ”)
1025	Abstract for Pena Peloché et al., <i>Treatment Of Severe And Persistent Food Allergy With Omalizumab</i> , J. ALLERGY CLIN. IMMUNOL. (Feb. 2011), (“ <i>Peloché Abstract</i> ”)
1027	Rui Zhu et al., <i>Pharmacokinetics and exposure-efficacy relationships of omalizumab in patients with nasal polyps</i> , 71 PULMONARY PHARMACOLOGY & THERAPEUTICS 1-12 (Sept. 28, 2021) (“ <i>Zhu</i> ”)
1028	Crisoforo Incorvaia et al, <i>Current and future applications of the anti-IgE antibody omalizumab</i> , 2 BIOLOGICS: TARGETS & THERAPY 1:67-73 (2008) (“ <i>Incorvaia</i> ”)
1029	Alessandro Fiocchi et al., <i>Impact of Omalizumab on Food Allergy in Patients Treated for Asthma: A Real-Life Study</i> , J. ALLERGY CLIN. IMMUNOL. PRACT.7:1901-9 e5 (2019) (“ <i>Fiocchi 2019</i> ”)
1030	Alessandro Fiocchi et al., <i>The use of biologics in food allergy</i> , 51 CLIN. EXP. ALLERGY 1006-1018 (2021) (“ <i>Fiocchi 2021</i> ”)
1031	Hugh A. Sampson et al., <i>A phase II, randomized, double-blind, parallel-group, placebo-controlled oral food challenge trial of Xolair (omalizumab) in peanut allergy</i> , 127 J. ALLERGY CLIN. IMMUNOL. 5:1309-10 e1 (Mar. 11, 2011) (“ <i>Sampson</i> ”)
1032	Jessica H. Savage et al., <i>Kinetics of mast cell, basophil, and oral food challenge responses in omalizumab-treated adults with peanut allergy</i> , 130 J. ALLERGY CLIN. IMMUNOL. 5:1123-9 e2 (Nov. 2012) (“ <i>Savage</i> ”)

Exhibit No.	Description
1035	Francesca Mori et al, <i>Oral Immunotherapy for Food-Allergic Children: A Pro-Con Debate</i> , 12 FRONTIERS IN IMMUNOL. 1-15 (Sept. 2021) (“Mori”)
1036	Caroline Nilsson et al., <i>Successful management of severe cow’s milk allergy with omalizumab treatment and CD-sens monitoring</i> , ASIA PACIFIC ALLERGY 4:257-260 (2014) (“Nilsson”)
1037	Sara Manti et al., <i>Monoclonal Antibodies in Treating Food Allergy: A New Therapeutic Horizon</i> , NUTRIENTS 13:2314 (2021) (“Manti”)
1038	Matthias Volmar Kopp, <i>Omalizumab: Anti-IgE Therapy in Allergy</i> , CURR. ALLERGY ASTHMA REP. 11:101-106 (2011) (“Kopp”)
1039	Masaya Takahashi et al., <i>Oral immunotherapy combined with omalizumab for high-risk cow’s milk allergy: a randomized controlled trial</i> , NATURE SCIENTIFIC REPORTS 7:17453 (Dec. 12, 2017) (“Takahashi”)
1040	C. Martorell-Calatayud et al., <i>Anti-IgE-assisted desensitization to egg and cow’s milk in patients refractory to conventional oral immunotherapy</i> , 27 PEDIATR. ALLERGY IMMUNOL. 5:544-46 (May 6, 2016) (“Martorell-Calatayud”)
1041	Imad Neal Saab et al., <i>Trends in Food Allergy Research, Regulations and Patient Care</i> , 57 NUTRITION TODAY 2:64-68 (March/April 2022) (“Saab”)
1042	Ruchi S. Gupta et al., <i>The Public Health Impact of Parent-Reported Childhood Food Allergies in the United States</i> , 142 Pediatrics 6: e20181235, (Dec. 2018) (“Gupta”)
1043	Giuseppe Crisafulli et al, <i>Omalizumab in children with severe allergic disease: a case series</i> , 45 ITALIAN J. PEDIATRICS 1:13 (Jan. 14, 2019) (“Crisafulli”)
1044	Arnau Navinés-Ferrer et al., <i>IgE-Related Chronic Diseases and Anti-IgE-Based Treatments</i> , 2016 J. IMMUNOL. RES. (Dec. 21, 2016) (“Navinés-Ferrer”)
1045	Marc Humbert et al., <i>IgE-Mediated Multimorbidities in Allergic Asthma and the Potential for Omalizumab Therapy</i> , 7 J. ALLERGY CLIN. IMMUNOL. PRACT. 5:1418-1429 (2019) (“Humbert”)
1046	Thomas Sandström, <i>Omalizumab in the management of patients with allergic (IgE-mediated) asthma</i> , 2009 J. ASTHMA & ALLERGY 2:49-62 (May 5, 2009) (“Sandström”)

Exhibit No.	Description
1047	Sankei Nishima et al., <i>Omalizumab and unmet needs in severe asthma and allergic comorbidities in Japanese children</i> , 9 ASIA PACIFIC ALLERGY 1:e7, 1-13 (Jan. 2019) (“Nishima”)
1048	Sandra Andorf et al., <i>A Phase 2 Randomized Controlled Multisite Study Using Omalizumab-facilitated Rapid Desensitization to Test Continued vs Discontinued Dosing in Multifood Allergic Individuals</i> , 7 ECLINICALMEDICINE 27-38 (2019) (“Andorf 2019”)
1049	Donald Y.M. Leung et al., <i>Effect of Anti-IgE Therapy in Patients with Peanut Allergy</i> , N ENGL. J. MED. 348:986-93 (2003) (“Leung”)
1050	XOLAIR® Omalizumab, FOOD AND DRUG ADMINISTRATION (2003) (“PI2003”)
1051	XOLAIR® Prescribing Information, FOOD AND DRUG ADMINISTRATION (July 2016) (“PI2016”)
1052	Philip J. Lowe, <i>Revision of omalizumab dosing table for dosing every 4 instead of 2 weeks for specific ranges of bodyweight and baseline IgE</i> , 71 Regulatory Toxicology and Pharma. 68-77 (2015) (“Lowe”)
1053	National Institutes of Health, <i>Press Release: National Institutes of Health Launches “ClinicalTrials.gov”</i> , U.S. NATIONAL LIBRARY OF MEDICINE (February 29, 2000), https://www.nlm.nih.gov/archive/20040831/news/press_releases/clntrlpr00.html (“NLM Press Release”)