

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

VALNEVA AUSTRIA GMBH,

Petitioner

v.

TAKEDA VACCINES, INC.,

Patent Owner

Case IPR2025-00776
U.S. Patent No. 11,730,802

**DECLARATION OF DR. DAN H. BAROUCH, M.D., Ph.D., IN SUPPORT
PATENT OWNER'S PRELIMINARY RESPONSE**

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Takeda Vaccines EX2026
IPR2025-00776
U.S. Patent No. 11,730,802

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I, Dan H. Barouch, hereby declare as follows.

I. INTRODUCTION

1. I am over the age of eighteen and competent to make this declaration.

2. I have been retained as an expert witness on behalf of Takeda Vaccines, Inc. (“Takeda”) for the above-captioned *inter partes* review (“IPR”).

I am being compensated for my time in connection with this IPR at my standard consulting rate, which is \$1,500.00 per hour.

3. I understand that this Declaration accompanies Takeda’s Preliminary Patent Owner’s Response to a Petition for Inter Partes Review of U.S. Patent No. 11,730,802 (“the ’802 patent”) (EX1001) filed by Valneva Austria GmbH (“Valneva”). I also understand that the ’802 patent is currently assigned to Takeda. Generally, the ’802 patent relates to Zika virus (“ZIKV”) vaccines. ZIKV is a member of the family of viruses known as *Flaviviridae*. Other viruses in this family include Yellow Fever virus (“YFV”), Tick-Borne Encephalitis virus (“TBEV”), Japanese Encephalitis virus (“JEV”), and Dengue virus (“DENV”). All of these viruses also belong to the genus of viruses known as flaviviruses.

4. I understand that the ’802 patent resulted from U.S. Patent Application No. 16/761,329 (“the ’329 application”), filed on May 4, 2020, as stated on the ’802 patent’s face page. EX1001. I understand that the ’329 application is the US national stage application of international application

PCT/US2018/059233 (“the ’233 PCT”) published as WO 2019/090238 and filed November 5, 2018. The ’802 Patent also claims priority to U.S. provisional application No. 62/592,995 filed November 30, 2017 and U.S. provisional application No. 62/581,500 filed November 3, 2017.

5. In preparing this Declaration, I have reviewed the ’802 patent, its file history, and the documents cited in paragraph 36.

6. I understand that Takeda statutorily disclaimed claims 1–8, 10, 12–31, 59, and 63 on June 11, 2025. EX2005, 3. Thus, I understand that disclaimed claims 1–8, 10, 12–31, 59, and 63, and therefore Grounds I and III–VI, are not currently part of this IPR proceeding.

7. I further understand that claims 9, 11, 32–62, and 64–67 (“Challenged Claims”) remain at issue in this proceeding, as challenged in Grounds II and VII–XI.

II. MY BACKGROUND AND QUALIFICATIONS

8. I am an expert in the field of virology and vaccinology, including the immunology and pathogenesis of viral infections and the development of novel vaccine and treatment strategies. My expertise includes the development of vaccine candidates for multiple pathogens of global significance, including HIV-1, ZIKV, SARS-CoV-2, influenza, and tuberculosis. I participated in the development of a SARS-CoV-2 vaccine, which led to the Janssen/Johnson & Johnson COVID-19

vaccine (Ad26.COV2.S) that received Emergency Use Authorization from the United States Food & Drug Administration in February 2021 and multiple approvals throughout the world. I also participated in the development of two ZIKV vaccines that were advanced into clinical trials. I have actively been working in the vaccinology, virology, and immunology fields since 1995.

9. In 1993, I received a Bachelor of Arts in Biochemistry, graduating *summa cum laude*, from Harvard University in Cambridge, Massachusetts. In 1995, I obtained a Doctor of Philosophy in Immunology from Oxford University in Oxford, England. I also received my Doctor of Medicine, *summa cum laude*, from Harvard Medical School in 1999 in Boston, Massachusetts.

10. From 1996 to 2002, I was a Research Fellow at the Beth Israel Deaconess Medical Center in Boston, Massachusetts. In the period from 1999 to 2001, I was also an Intern and Resident in Medicine at the Massachusetts General Hospital in Boston, Massachusetts. From 2001 to 2004, I was a Fellow in Infectious Diseases at Massachusetts General Hospital and Brigham and Women's Hospital.

11. Since 2001, I have also held Physician appointments at hospitals and affiliated institutions, including Massachusetts General Hospital, Brigham and Women's Hospital, Dana-Farber Cancer Institute, and currently at Beth Israel Deaconess Medical Center. In 2012, I was the Founding Director of the Center of

Virology and Vaccine Research at Beth Israel Deaconess Medical Center, a position that I have held for the past 13 years.

12. Since 2002, I have held Instructor, Assistant Professor, Associate Professor, and Professor appointments at Harvard Medical School. I have also taught classes at Harvard College, Harvard School of Public Health, and Massachusetts Institute of Technology. Currently, I am the William Bosworth Castle Professor of Medicine at Harvard Medical School.

13. I have authored or co-authored over 400 published, peer-reviewed articles, as well as numerous abstracts and presentations, most of which are related to vaccinology, immunology, or virology.

14. In addition to my educational training and professional and research experiences described above, I have kept abreast of the fields of vaccinology, virology, and immunology by reading scientific literature; conferring with colleagues in the field; attending, presenting, and leading scientific conferences; and delivering regular and invited lectures.

15. Since 2004, I have served in an editorial capacity for several scientific journals including: Journal of Virology, Journal of Infectious Diseases, Clinical and Experimental Immunology, and Journal of Immunology. I have also served as a peer reviewer for several scientific journals including: Blood, Journal of Virology, Virology, Science, Nature Medicine, Nature Reviews Immunology,

Journal of Infectious Diseases, Nature, Clinical Infectious Diseases, Journal of General Virology, Journal of Immunology, Nature Immunology, Clinical Vaccine and Immunology, Proceedings of the National Academy of Sciences, New England Journal of Medicine, Cell, Lancet Infectious Diseases, and Lancet.

16. Starting in early 2016, my research group began work on developing a ZIKV vaccine. This led to a collaboration with researchers at the Walter Reed Army Institute of Research (WRAIR) in Silver Spring, MD to develop and test vaccines against ZIKV. One of these vaccines developed in collaboration with WRAIR was a purified inactivated ZIKV vaccine that stimulated neutralizing antibodies and conferred protection against ZIKV when administered to mice and rhesus monkeys. EX2003, 476, Table 1, FIG. 4; EX2004, 1129, FIGS.1, 2, S1–S6. Data from those studies is included in the Thomas patent application publication (EX1004) relied upon and cited extensively by Dr. Guirakhoo. EX1004, FIGS. 7–13. I also collaborated with Janssen in the development of an Ad26 vector-based ZIKV vaccine candidate, which was evaluated in mice, rhesus monkeys, and humans.

17. Accordingly, I am an expert in the fields of virology and vaccinology, including vaccines for ZIKV. For that reason, I am qualified to provide an opinion as to what a person of ordinary skill in the art (“POSA”) would have understood, known, or concluded as of the dates referenced herein.

III. PERSON OF ORDINARY SKILL IN THE ART

18. As an expert, I have offered opinions throughout this declaration from the perspective of a POSA. I understand that the level of ordinary skill in the art acts as a lens through which the prior art and claimed invention must be viewed. I understand that a POSA is a hypothetical person who is presumed to be aware of all pertinent art, thinks along conventional wisdom in the art, and is a person of ordinary creativity. I also understand that the following factors are pertinent to the determination of the level of ordinary skill: (1) the educational level of the inventor(s), (2) the type of problems encountered in the art, (3) the prior art solutions to those problems, (4) the rapidity with which innovations are made, (5) the sophistication of the technology, and (6) the educational level of active workers in the field.

19. A POSA relevant to the '802 patent would have had skills and knowledge of the scientific literature related to virology, including flaviviruses, and vaccines and have had skills relating to methods for developing and testing viral vaccines, including flavivirus vaccines. A POSA also would have had skills and knowledge regarding laboratory techniques and strategies for passaging viruses, designing vaccines, conducting *in vitro* studies testing and analyzing immune responses to vaccines, and performing and interpreting preclinical and clinical vaccine studies.

20. Typically, a POSA would have had an M.D. and/or a Ph.D. degree, specializing in infectious diseases, virology, immunology, vaccinology, or a related discipline (e.g., biology, molecular biology, biochemistry, microbiology, structural biology, pathology), as well as, typically, at least 3 years of research and development experience specializing in developing and testing antiviral vaccines.

21. A POSA may also have worked as part of a multi-disciplinary team with experience in researching, designing, developing, and testing antiviral vaccines. For instance, such a team may be comprised of a clinician, epidemiologist, microbiologist, and/or a biostatistician.

22. Dr. Guirakhoo opines, with respect to the '802 patent, that

A person of ordinary skill in the art would have an M.D. or Ph.D. degree in virology, immunology, or vaccinology and at least 3 years of experience in one or more of the research, design, development and testing of antiviral vaccines. One of skill in the art may be part of a multidisciplinary team having experience in one or more of the research, design, development and testing of antiviral vaccines.

EX1002, ¶81. My opinions herein would remain that same under either Dr. Guirakhoo's or my definition of a POSA.

IV. LEGAL BASIS FOR MY ANALYSIS

23. In formulating my opinions set forth in this Declaration, I applied the following legal principles.

A. Claim Construction

24. I understand that in an IPR, patent claim terms are given their ordinary and customary meaning as understood by a POSA at the time of the invention, in view of the patent's specification and its prosecution history—unless the patent explicitly defines the claim term. I also understand that when a patent explicitly defines a claim term in the specification, the patent's definition controls.

25. I understand that claims 1, 9, 11, 26, 41, 43, 49, 53, 54, 57, and 58 are the independent claims in the '802 patent. I understand that claims 2–8, 10, 12–25, 27–31, and 59 depend either directly or indirectly from claim 1. I understand that claims 32–40, 44–48, 55, 56, and 65–67 depend either directly or indirectly from claim 9. I understand that claims 60–62 depend directly from claim 11. I understand that claim 63 depends directly from claim 26. I understand that claim 42 depends directly from claim 41. I understand that claims 50–52 depend directly from claim 49. I understand that claim 64 depends directly from claim 54.

26. I understand that Takeda statutorily disclaimed claims 1–8, 10, 12–31, 59, and 63 on June 11, 2025. EX2005, 3. Thus, I understand that disclaimed claims 1–8, 10, 12–31, 59, and 63, and therefore Grounds I and III–VI, are not currently part of this *inter partes* review proceeding.

27. I further understand that claims 9, 11, 32–62, and 64–67 (“Challenged Claims”) remain at issue in this proceeding, as challenged in Grounds II and VII–XI.

28. I understand that a dependent claim contains all limitations of the claim(s) from which it depends. I, therefore, understand that claims 32–40, 42, 44–48, 50–52, 55, 56, 60–62, and 64–67 contain all the limitations of the claims from which they either indirectly and/or directly depend, as set forth in paragraph 25.

B. Anticipation

29. I understand that a prior art reference anticipates a claim if it

- (i) discloses each and every element recited in the claim, arranged as claimed and
- (ii) enables a POSA to make and use the subject matter that anticipates the claim. I understand that for the purposes of anticipation the prior art reference only need to enable a single embodiment that anticipates the claims at issue. I additionally understand that a reference can anticipate even if it does not expressly spell out all the limitations arranged or combined as in the claim, if a POSA, reading the reference would at once envisage the claimed arrangement or combination.

C. Obviousness

30. I understand that an obviousness analysis involves comparing a claim with the prior art to determine whether the claimed subject matter would

have been obvious to a POSA in view of the asserted prior art and the general knowledge in the background art. I understand that obviousness must be assessed from the viewpoint of a POSA at the time of the invention, which here is prior to November 3, 2017.

31. I understand that, in determining the scope and content of the prior art and ascertaining the differences between the claimed invention, a patent challenger must specify where each element of the claim is found in the prior art.

32. I understand that combining or modifying the teachings of the prior art to achieve the claimed invention is a way to establish obviousness. I understand that the reason to combine prior art references can come from a variety of sources, not just the prior art itself or the specific problem the patentee was trying to solve. And I understand that the references themselves need not provide a specific hint or suggestion of the alteration needed to arrive at the claimed invention; the analysis may include recourse to logic, judgment, and common sense available to a person of ordinary skill that does not need to be explicit in any reference.

33. I understand that one way of establishing obviousness is by establishing that a POSA would have had both (i) a reason to modify or combine the prior art to achieve the claimed invention; and (ii) a reasonable expectation of success in so doing. I understand that this does not require absolute predictability of success.

34. I further understand that a claimed range may be obvious if a prior art reference discloses a range that overlaps with or is encompassed by the claimed range. I further understand that even if a prior art reference does not disclose a particular value or range of values, the prior art can still render a claim obvious if it would require only routine experimentation to arrive at the claimed value or range of values. I understand that experimentation may be “routine” where a POSA would have had a reasonable expectation of success in optimizing the value and would only need to use well-known problem-solving strategies to verify that expectation. I understand that for routine experimentation to be applicable a particular parameter must first be recognized as a result-effective variable, which I understand is a variable that achieves a recognized result, before the determination of the optimum or workable ranges of the variable may be characterized as routine experimentation. I also understand that evidence of teaching away, unexpected results, and/or criticality, or other pertinent objective evidence may be presented to indicate that the overlapping range would not have been obvious in light of the prior art.

35. I also understand that, before reaching a conclusion that the claimed invention would have been obvious, one must consider any objective evidence of nonobviousness if it is available. I understand that objective evidence of nonobviousness (also known as secondary considerations of nonobviousness)

includes evidence of commercial success attributable to the claimed invention, evidence of industry praise for the claimed invention, evidence of a long-felt need that was solved by the claimed subject matter, evidence that others copied the claimed subject matter, or evidence that the claimed subject matter achieved an unexpected, superior result relative to the closest prior art. I understand that such evidence must have a nexus, or causal relationship, to the claimed subject matter beyond what was available in the prior art, and must be commensurate in scope with the patent claim(s) at issue. I also understand that near-simultaneous invention by another is evidence of the level of skill in the art and constitutes objective evidence that POSAs understood the problem and its solution.

V. DOCUMENTS CONSIDERED IN FORMULATING MY OPINIONS

36. I have been asked to opine from the perspective of a POSA on whether the Examiner considered the same or substantially the same art and arguments as now presented by Dr. Guirakhoo, and on the merits of certain arguments by Dr. Guirakhoo's Declaration. In providing my testimony, I considered the documents cited in this Declaration and the documents listed in the table below.

Exhibit No.	Description
1001	U.S. Patent No. 11,730,802
1002	Expert Declaration of Dr. Guirakhoo

Exhibit No.	Description
1003	Excerpted File History of the '802 patent
1004	Thomas WO 2017/210215 (Thomas)
1005	Barbero WO 2017/109223 (Barbero)
1006	Murata et al., "Plaque purification as a method to mitigate the risk adventitious-agent contamination in influenza vaccine virus seeds," <i>Vaccine</i> , 2011 Apr 12;29(17):3155-61 (Murata)
1007	Faucette et al., "Immunization of pregnant women: Future of early infant protection," <i>Human Vaccines & Immunotherapeutics</i> 11:11, 2549-2555; November 2015 (Faucette)
1008	PCT/US2018/059233 (published as WO2019/090238)
1009	Provisional application No. 62/592,995
1010	Provisional application No. 62/581,500
1011	Version 8 of Clinical Trial NCT02952833
1012	Liu, et al., Clinical and Vaccine Immunology, Vol. 19, No. 1 (January 2012) pp. 73-78
2003	Larocca, R.A., et al., "Vaccine Protection Against Zika Virus from Brazil," <i>Nature</i> , 536: 474-478 (2016)
2004	Abbink, P., "Protective Efficacy of Multiple Vaccine Platforms Against Zika Virus Challenge in Rhesus Monkeys," <i>Science</i> , 353(6304) 1129-1132 (2016)
2005	Statutory Disclaimer for U.S. Patent No. 11,730,802, Filed June 11, 2025
2006	Sumathy et al., "Protective efficacy of Zika vaccine in AG129 mouse model," <i>Scientific Reports</i> , 7:46375, 1-9; April 12, 2017 (Sumathy)
2007	Wressnigg et al., "A randomized, placebo-controlled, blinded phase 1 study investigating a novel inactivated, Vero cell-culture derived Zika virus vaccine," <i>Journal of Travel Medicine</i> , 1-10; (2022) (Wressnigg)

Exhibit No.	Description
2008	Burton, D.R., “Antibodies, Viruses and Vaccines,” <i>Nature Review Immunology</i> , 2: 706–713 (2002)
2009	Roehrig, J.T., et al., “Guidelines for Plaque-Reduction Neutralization Testing of Human Antibodies to Dengue Viruses,” <i>Viral Immunology</i> , 21(2): 123–132 (2008)
2010	Martinez, L.J., et al., “Safety and Immunogenicity of a Dengue Virus Serotype-1 Purified-Inactivated Vaccine: Results of a Phase 1 Clinical Trial,” <i>Am. J. Trop. Med. Hyg.</i> , 93(3): 454–460 (2015) (Martinez)
2011	Srivastava, A.K., et al., “A Purified Inactivated Japanese Encephalitis Virus Vaccine Made in Vero cells,” <i>Vaccine</i> , 19(3): 4557–4565 (2001)
2012	Thomas, S. J., et al., “A Phase II, Randomized, Safety and Immunogenicity Study of a Re-derived, Live-attenuated Dengue Virus Vaccine in Healthy Adults,” <i>Am. J. Trop. Med. Hyg.</i> , 88(1): 73–88 (2013) (Thomas II)
2013	Shan, C., “Zika Virus: Diagnosis, Therapeutics, and Vaccine,” <i>ACS Infectious Diseases</i> , 2: 170–172 (2016)
2014	Christopher J. Burrell, Fenner and White’s Medical Virology 155-167 (5th ed. 2016)
2015	Monath, T, et al., “An Inactivated Cell-Culture Vaccine against Yellow Fever,” <i>N Engl J Med</i> , 364:1326-33 (2011) (Monath)
2016	Label for IXIARO® (Japanese Encephalitis Vaccine, Inactivated, Adsorbed), (Jul. 23, 2017), available at: https://wayback.archive-it.org/7993/20170722072912/https://www.fda.gov/downloads/BiologicalsBloodVaccines/Vaccines/ApprovedProducts/UCM142569.pdf (last accessed June 2, 2025)
2017	Schöendorf, I., et al., “Tick-borne encephalitis (TBE) vaccination: Applying the most suitable vaccination schedule,” <i>Vaccine</i> , 25:1470-1475 (2007) (Schöendorf)

Exhibit No.	Description
2018	Legrand, N., et al., “Humanized Mice for Modeling Human Infectious Disease: Challenges, Progress, and Outlook,” <i>Cell Host & Microbe</i> , 6:5-9 (2009)
2019	Rasmussen, S.A., “Vaccines and Pregnancy: Past, Present, and Future,” <i>Seminars in Fetal & Neonatal Med.</i> , 19: 161–169 (2014) (Rasmussen)
2020	Rasmussen, S.A., et al., “Zika Virus and Birth Defects — Reviewing the Evidence for Causality,” <i>N Engl J Med</i> , 374:1981–87 (2016) (Rasmussen II)
2021	Davis, M., “A Prescription for Human Immunology,” <i>Immunity</i> , 29:835–838 (2008)
2022	McNeela, E. A. & Mills, K. H., “Manipulating the immune system: humoral versus cell-mediated immunity,” <i>Adv Drug Deliv Rev.</i> , 51(1–3):43–54 (2001)
2023	Manikandan, S., “Measures of central tendency: The mean,” <i>Journal of Pharmacology and Pharmacotherapeutics</i> , 2(2):140–142 (2011)
2024	Shedlock, et al., “Monkeying around with HIV vaccines: using rhesus macaques to define 'gatekeepers' for clinical trials,” <i>Nature Reviews Immunology</i> , 9:717-728 (2009)
2025	Paul A. Offit, “Pandora’s Lab: Seven Stories of Science Gone Wrong,” 213–240 (April 4, 2017).
2027	Tao, L. & Reese, T.A., “Making Mouse Models That Reflect Human Immune Responses,” <i>Trends in Immunology</i> , 38(3):181–193 (March 2017)
2029	Khun, K.A. & Stappenbeck, T.S., “Peripheral Education of the Immune System by the Colonic Microbiota,” <i>Seminars in Immunology</i> , 25:364–369 (2013)
2030	Beura, L.K., et al., “Normalizing the Environment Recapitulates Adult Human Immune Traits in Laboratory Mice,” <i>Nature</i> , 532:512–518 (2016)

Exhibit No.	Description
2031	Miner, J.J., et al., “Zika Virus Infection during Pregnancy in Mice Causes Placental Damage and Fetal Demise,” <i>Cell</i> , 165:1081–1091 (2016)
2032	Cugola, F.R., et al., “The Brazilian Zika virus strain causes birth defects in experimental models,” <i>Nature</i> , 534:267–273 (2016)
2033	Adams Waldorf, K.M., et al., “Fetal brain lesions after sub-cutaneous inoculation of Zika virus in a pregnant nonhuman primate,” <i>Nature Medicine</i> , 22(11):1256–1261 (2016)
2034	Walpole, S.C., et al., “The weight of nations: an estimation of adult human biomass,” <i>BMC Public Health</i> , 12(439):1–6 (2012)
2035	Good, K.L., et al., “Decreased expression of Kruppel-like factors in memory B cells induces the rapid response typical of secondary antibody responses,” <i>PNAS</i> , 104(33):13420–13425 (2007)
2036	Murphy, K., “Janeway’s Immunobiology,” (8th ed., 2012), Chapter 11
2037	Sallusto, F., et al., “From vaccines to memory and back,” <i>Immunity</i> , 33:451–463 (2010)
2038	Sörman, A., et al., “How antibodies use complement to regulate antibody responses,” <i>Molecular Immunology</i> , 61:79–88 (2014)
2039	“Body Weight Information for BALBc,” The Jackson Laboratory, accessible at https://www.jax.org/jax-mice-and-services/strain-data-sheet-pages/body-weight-chart-000651 (last accessed July 10, 2025)
2040	Teixeira, F. M. E., et al., “Maternal-Fetal Interplay in Zika Virus Infection and Adverse Perinatal Outcomes,” <i>Frontiers in Immunology</i> , 11(175):1–15 (2020)
2041	Babe, I. B., et al., “Interim Guidance for Interpretation of Zika Virus Antibody Test Results,” <i>Morbidity and Mortality Weekly Report, CDC</i> , 65(21):543–546 (2016)
2042	Wren, L., et al., “Influence of Cytokines on HIV-Specific Antibody Dependent Cellular Cytotoxicity Activation Profile of Natural Killer Cells,” <i>PLOS One</i> , 7(6):1–9 (2012)

Exhibit No.	Description
2043	Raghupathy, Raj, “Cytokines as Key Players in the Pathophysiology of Preeclampsia,” <i>Medical Principles and Practice</i> , 22(Suppl. 1):8–19 (2013)

VI. DR. GUIRAKHOO’S PROPOSED GROUNDS

37. Dr. Guirakhoo has alleged that the Challenged Claims are allegedly unpatentable over the followings Grounds that I understand are still at issue in this proceeding:

Grounds	Claims	Prior Art
Ground II	11, 60, 61, and 62	Thomas (EX1004)
Ground VII	9, 32, 33, 35, 36, 38, 39, 41, 47, 49, 51, 55–58, and 65–67	Thomas, Faucette (EX007)
Ground VIII	34, 43–46, and 48	Thomas, Faucette, NCT02952833 (EX1011)
Ground IX	37, 40, 42, 50, and 52	Thomas, Faucette, Barbero (EX1005)
Ground X	54 and 64	Thomas, Faucette, NCT02952833, Barbero
Ground XI	53	Thomas, Faucette, Murata (EX1006)

VII. THE ’802 PATENT AND ITS CLAIMS

38. The ’802 patent is directed to “Zika virus vaccines and immunogenic compositions having one or more antigens from a Zika virus.” EX1001, Abstract.

ZIKV is a flavivirus classified with other mosquito-borne viruses such as YFV, TBEV, JEV, and DENV. EX1001, 1:41–43.

39. Claims 9, 32–58, and 64–67 are generally directed to a “method of vaccinating” a fetus or a newborn against ZIKV by administering a vaccine or immunogenic composition comprising an inactivated ZIKV virus vaccine to a pregnant human subject, wherein the pregnant human subject adoptively transfers a vaccine effective amount of neutralizing antibodies against ZIKV to the fetus or newborn. EX1001, 123:24–34, 125:41–49, 125:24–64, 126:14–24, 126:36–58, 127:9–19. I may refer herein collectively to claims 9, 32–58, and 64–67 as “the Fetal Protection Claims.”

40. Claim 11 and 60–62 are directed to a method of vaccinating against ZIKV infection in a human subject by a single dose or prime administration, i.e., after a single injection of an inactivated ZIKV vaccine, inducing a seroconversion rate of at least 60% (claim 11), at least 80% (claim 60), at least 90% (claim 61), and at least 95% (claim 62) after 14 and/or 28 days of the administration of the single dose or prime administration. EX1001, 123:40–52. Claims 39 and 65–67 also require inducing a seroconversion rate of at least 60% (claim 39), at least 70% (claim 65), at least 80% (claim 66), and at least 90% (claim 67) after 14 and/or 28 days of the administration of a single dose or prime administration of an inactivated ZIKV vaccine. EX1001, 128:13–26. I may refer herein collectively to

claims 11, 39, 60–62, and 65–67 as “the Single Dose/Prime Administration Claims.”

VIII. TECHNICAL CONSIDERATIONS FOR THE '802 PATENT

41. I present below a brief summary of various technical considerations that a POSA would have understood before November 3, 2017, with regard to what a POSA would have known about various characteristics of vaccines, ZIKV, and other known inactivated flavivirus vaccines.

A. Brief Technical Background On Vaccines

42. The goal of vaccination is to stimulate the vaccinated subject's immune system, including generating antibodies that neutralize the infectious agent, such as viruses, to prevent or treat infection or limit the consequences of infection. EX2008, 709. The art provided that the amount, i.e., “titer,” of antibodies that neutralize the infectious agent, i.e. “neutralizing antibodies,” arising after vaccination could be determined by an assay that involves mixing infectious virus with the serum of vaccinated subjects and observing the ability of antibodies present in the serum to prevent infection of mammalian cells in vitro. EX2009, 126.

43. If neutralizing antibodies above a certain predetermined cut-off are detected that indicate a significant immune response in the vaccinated subject, a POSA would determine that the subject had been considered seroconverted. *See*,

e.g., EX1004, 39:14–15, 41:30–31 (using neutralizing antibody titers of $> 1:10$ as indicative of seroconversion and stating that neutralizing antibody titers of $> 1:10$ “have been reported for other flavivirus vaccines in humans”); EX2016, 20 (using neutralizing antibody titers of $\geq 1:10$ as indicative of seroconversion); EX2010, Table 3 (same); EX2015, Table 2 (using a neutralizing titers of $\geq 1:20$ as indicative of seroconversion). By analyzing multiple subjects of a vaccinated population, a POSA could determine the seroconversion rate after vaccination.

44. Before November 3, 2017, different types of approved vaccines known to elicit different levels of immune response after an initial dosing were known in the art, such as live-attenuated vaccines and inactivated virus vaccines. EX2012, EX1004, EX2013, 171.

1. Live-attenuated virus vaccines and inactivated virus vaccines typically induce different levels of immune responses.

45. Before November 3, 2017, it was known that different types of vaccines, such as live-attenuated virus vaccines and inactivated virus vaccines, typically induced different levels of immune responses after the first dose. EX2012; EX1004; EX2013, 171.

46. Live-attenuated vaccines use a weakened (“attenuated”) version of the virus that can stimulate an immune response. EX2014, 164. These types of vaccines typically could provide a significant immune response after one dose.

EX2013, 171. One reason for this effect is because the live-attenuated virus in those vaccines can continue to replicate in the recipient. EX2014, 156. This replication of the live-attenuated virus results in amplifying the amount of antigen available for presentation to the recipient's immune system and prolonging the exposure of the immune system to the antigen. EX2014, 156.

47. Live-attenuated viruses, moreover, would also not have been subjected to possible damages of antigenic proteins in the virus as a result of the inactivation process. EX2014, 158. Therefore, significant amounts of the antigen are preserved and presented to the recipient's immune system in a single dose of live-attenuated virus vaccine, which typically allows the immune system to produce a generally robust response against the antigen and, in turn, against the targeted virus. EX2014, 156.

48. In contrast, inactivated virus vaccines were typically not known in the art to provide a significant immune response after a single dose compared to live-attenuated vaccines. This is largely because the virus in such inactivated virus vaccines cannot replicate. EX2014, 156. As a result, a single dose of inactivated virus vaccine typically produces a lower immune response than a single dose of live-attenuated virus vaccines. EX2014, 158.

49. Inactivated virus vaccines are generally considered safer than live-attenuated viruses because the inactivation process "destroy[s] infectivity while

retaining immunogenicity.” EX2014, 158. However, this process comes at a cost.

The downside of this process has been that the “treatment used to eliminate infectivity of inactivated virus vaccines may be damaging enough to modify immunogenicity” by damaging the virus’s proteins that act as antigens, which impair the virus proteins’ ability to elicit immune responses. EX2014, 158. This results in “an immune response shorter in duration, narrower in spectrum for viral antigens, weaker cell-mediated and mucosal immune responses¹, and possibly less effective in preventing viral entry [into cells].” EX2014, 158. Vaccination with inactivated virus vaccines, therefore, minimally “comprises two or three injections; further ‘booster’ doses may be required at intervals to maintain protective immunity.” EX2014, 158.

2. The primary immune response is generally lower after the first dose of a vaccine compared to the heightened immune response to a second and subsequent doses.

50. The first exposure to an antigen results in the subject’s primary immune response. EX2035, 13420; EX2036, 429. The body’s immune system recognizes the antigen as “new” and produces neutralizing antibodies against the

¹ Cell-mediated immune responses derive from the body’s T cell response to an antigen, and mucosal immune responses derive from mucosal delivery, e.g., oral, of an antigen. EX2022, 44.

antigen. EX2035, 13420; EX2037, 452–453; EX2036, 429. In this primary immune response—which can take several weeks to develop—the immune system generates memory B and T cells that remain in the body for an extended period of time after the first exposure to an antigen. EX2035, 13420; EX2037, 452–453, 455.

51. Due to the memory B and T cells generated by the primary immune response, the immune system generally mounts a more rapid and effective response to the antigen when the subject is exposed to the antigen for the second time, which is known as the “anamnestic,” or secondary, response. EX2037, 451; EX2036, 448–449, 451–455. The anamnestic response occurs when the memory B or T cells encounter the antigen for a second time, which generally leads to a rapid activation of the memory B or T cells. EX2037, 451; EX2036, 448–449, 451–455. The rapid activation then leads to higher immune responses, including neutralizing antibodies, compared to the primary immune response. EX2035, 13423; EX2037, 451–452; EX2036, 450–452.

52. Booster doses of vaccines generally trigger anamnestic responses when given at least several weeks or months after the first dose. EX2037, 455. Administering the later, second dose generally leads to anamnestic secondary immune responses that include higher titers of neutralizing antibodies typically

with greater affinity to the vaccine antigen, providing improved immunity.

EX2036, 450–452.

B. Before November 3, 2017, Inactivated Flavivirus Vaccines Required More Than One Dose To Elicit a Sufficient Titer Of Neutralizing Antibodies In A Population Of Human Subjects.

53. As discussed above, ZIKV is a flavivirus classified with other mosquito-borne viruses such as YFV, TBEV, JEV, and DENV. EX1001, 1:41–43. Inactivated flavivirus vaccines for JEV, YFV, DENV, and TBEV had been developed before November 3, 2017. Single-dose administrations of such inactivated flavivirus vaccines failed to show at least a 60% seroconversion rate in populations of human subjects. EX2010, Table 3; EX2015, Table 2; EX2016, 20; EX2017, 1471–1472.

54. The table below shows inactivated flavivirus vaccines investigated before November 3, 2017 and their seroconversion rates in humans as determined using a neutralizing antibody titer of at least 1:10, as had been used in the art for flavivirus vaccines. *See* ¶43, above.

Vaccine	Virus Type	Dose & Titer Cut-Off	Dose Administration Schedule	Seroconversion Rate % (1st dose)	Seroconversion rate % (2nd dose)
IXIARO (EX2016, 20)	JEV	6 µg Titer ≥ 1:10	First Dose – Day 0 Second Dose – Day 28	39.8% – measured 28 days after 1 st administration	97.3% – measured 7 days after 2 nd administration
XRX-001 (EX2015, Table 2)	YFV	4.8 µg Titer ≥ 1:20	First Dose – Day 0 Second Dose – Day 21	32% – measured 21 days after 1 st administration ²	100% – measured 10 days after 2 nd administration
DENV-1 PIV (EX2010, Table 3)	DENV	2.5 µg Titer ≥ 1:10	First Dose – Day 0 Second Dose – Day 28	11% (2.5 µg) – measured 28 days after 1 st administration	100% – measured 14 days after 2 nd administration

² At a cut-off titer of ≥ 1:10, which Monath used for indicating seropositivity, Monath only observed 46% of the human subject population as achieving that titer after a single administration. EX2015, Table 2.

Vaccine	Virus Type	Dose & Titer Cut-Off	Dose Administration Schedule	Seroconversion Rate % (1st dose)	Seroconversion rate % (2nd dose)
DENV-1 PIV (EX2010, Table 3)	DENV	5 µg Titer ≥ 1:10	First Dose – Day 0 Second Dose – Day 28	10% (5 µg) ³ – measured 28 days after 1 st administration	100% – measured 14 days after 2 nd administration
Encepur (Conv. Schedule; Group C) (EX2017, 1471– 1472)	TBEV	1.5 µg Titer ≥ 1:10	First Dose – Day 0 Second Dose – Day 28 Third Dose – Day 300	29% – measured 21 days after 1 st administration	95% – measured 14 days after 2 nd administration
Encepur (Modified Conv. Schedule; Group M)	TBEV	1.5 µg Titer ≥ 1:10	First Dose – Day 0 Second Dose – Day 21	28% – measured 21 days after 1 st administration	82% – measured 21 days after 2 nd administration

³ Martinez (EX2010) reports that 1 out of 10 subjects receiving either the 2.5 µg or 5 µg doses of its DENV-1 PIV vaccine demonstrated seroconversion after one dose, but reports the rates as 11% and 10%, respectively. EX2010, Table 3.

Vaccine	Virus Type	Dose & Titer Cut-Off	Dose Administration Schedule	Seroconversion Rate % (1st dose)	Seroconversion rate % (2nd dose)
(EX2017, 1471–1472) ⁴			Third Dose – Day 300		

55. In sum, inactivated flavivirus vaccines investigated in humans before November 3, 2017 required more than one dose to achieve a seroconversion rate of at least 60% in the vaccinated human population. Dr. Guirakhoo does not acknowledge any of the foregoing in his Declaration or explain how it colors his analysis, as discussed below in Section X.C.1. In fact, a POSA would have been aware of such information and would, therefore, not have had a reasonable

⁴ Schöndorf (EX2017) also evaluated further vaccination schedules with Encepur, i.e., a rapid schedule (Group R, vaccination on days 0, 7 and 21) and an accelerated conventional schedule (Group A, vaccination on days 0, 14 and 300). At Study Day 21, on which the seroconversion rate (cut-off 1:10) was determined for the first time, subjects in Groups R and A had already received the second dose. Notwithstanding receiving a second dose, the seroconversion rates remained below 60% (i.e., 56% and 53%, respectively). EX2017, 1472, FIG. 2.

expectation of developing an inactivated ZIKV vaccine that could achieve the claimed seroconversion rates in a population of human subjects after a single dose or prime administration.

C. ZIKV Was Known to Cause Congenital Birth Defects And A Single-Dose Inactivated Flavivirus Vaccine For Humans Had Eluded Vaccinologists Before November 3, 2017.

56. By November 3, 2017, a “hemispheric-wide epidemic” of ZIKV infection had spread throughout the Americas, including the U.S., since its introduction into Brazil in 2013. EX1001, 1:41–48. In late 2015, the virus prompted the World Health Organization (WHO) to declare a Public Health Emergency of International Concern. EX1001, 2:9–16.

57. ZIKV poses a significant threat, especially to pregnant women and the fetus. Prenatal ZIKV infection was known in the art to cause congenital defects by “crossing the placenta and targeting cortical neural progenitor cells.” EX2003, 474; *see also* EX2020, 1981, 1985. ZIKV infection in pregnant woman can have serious, negative effects, with infections leading to severe microcephaly and “catastrophic neurodevelopmental outcomes in human fetuses.” EX2031, 1084; EX2003, 474; EX2020, 1981–1983, 1985. While the risk of abnormal fetal development of the brain is highest after ZIKV infections earlier in pregnancy, ZIKV infections that occur later in pregnancy also have been associated with dramatic outcomes, including fetal death. EX2020, 1982. In fact, the art reported

that “ZIKV-induced fetal abnormalities can occur in all trimesters of pregnancy although the most severe manifestations are associated with infections in the first and second trimesters.” EX2031, 1081. Thus, vaccination at any pregnancy stage would have been important when seeking to protect against microcephaly and other birth defects.

58. The detrimental effects of a ZIKV infection in pregnant individuals would have made speed of onset of the subject’s immune response induced by a ZIKV vaccine, including production of a sufficient titer of neutralizing antibodies an important element of a ZIKV vaccine. Pregnant women would, therefore, have sought to protect themselves and their fetus against a possible ZIKV infection by quickly inducing a significant seroconversion rate, and with as few administrations as possible. In view of the results with other inactivated flavivirus vaccines, however, a POSA would have expected that an inactivated ZIKV vaccine would have also required multiple doses that are spread several weeks apart to induce sufficient seroconversion in a population of human subjects.

59. The threat from ZIKV was and is not limited to individuals living in countries with ZIKV outbreaks. “[B]rief periods of travel to countries with active Zika virus transmissions” by pregnant women had resulted in fetuses and infants with microcephaly. EX2020, 1983–1984. In 2016, various governments and public

health authorities advised pregnant women against traveling to areas with active ZIKV transmissions. EX2020, 1982.

60. Yet, before November 3, 2017, no single-dose, inactivated flavivirus vaccines for humans had been developed or described in the art, as discussed in Section VIII.B, above. And with regard to ZIKV, the Thomas patent application publication relied upon heavily by Dr. Guirakhoo shows the same for Thomas's inactivated ZIKV vaccine. ***Thomas's inactivated ZIKV vaccine had a negligible seroconversion rate after a single dose in humans and only achieved a seroconversion rate of at least 60% in the study's human subjects after administering a second dose.*** EX1004, 42:4–20. A POSA, therefore, would have expected multiple doses of inactivated ZIKV vaccines, administered at least several weeks apart, to be required to achieve sufficient seroconversion in human subjects, as discussed below in Sections X.A and X.C.1.

61. The claimed invention in the Challenged Claims of the '802 patent addresses the risk of ZIKV infection and transmission by providing methods of seroconverting at least 60% of a population of human subjects after a single dose or prime administration with an inactivated ZIKV vaccine and for vaccinating

against ZIKV disease in a fetus or newborn⁵ comprising administering an inactivated ZIKV vaccine to a pregnant human subject and transferring a vaccine effective amount of neutralizing antibodies from the pregnant human subject to the fetus or newborn. EX1001, 123:24–34, 40–52, 124:62–128:26. The claimed invention not only has the potential to provide protection to pregnant individuals or individuals who may become pregnant who reside in countries where ZIKV may be present, but it also has the potential to protect travelers and military personnel serving in these countries. EX1001, 8:2–7. The claimed methods are also beneficial for areas where there may be an unexpected outbreak of ZIKV, in which a sufficient immune response would be needed quickly, and with as few administrations as possible. In fact, as the '802 patent states, “high geometric mean neutralizing antibodies titers indicate an early onset of protection which is beneficial in an outbreak situation or [for] a traveler visiting an endemic area within a short period of time from the administration of the vaccine or immunogenic composition.” EX1001, 8:2–7.

⁵ Antibodies transferred during gestation persist in newborns for a period of time after birth. EX2019, 161.

62. Moreover, as ZIKV “may also be sexually transmitted,” individuals, such as travelers and military personnel in the affected countries, therefore, can bring ZIKV back and transmit the virus to others in the U.S. EX2013, 170.

IX. SUMMARY OF MY OPINIONS

63. As an expert, I have considered from the perspective of a POSA the contentions of Dr. Guirakhoo, as discussed in Sections X and XI, herein. As discussed below, a POSA would conclude that Dr. Guirakhoo’s contentions are substantively deficient because they are not adequately supported or grounded in the art Dr. Guirakhoo asserts against the Challenged Claims.

64. Specifically, Dr. Guirakhoo conflates the disclosures of Thomas and often makes conclusory statements that are not supported by citations or evidence or rely on hindsight. This is also true for statements made by Dr. Guirakhoo to support his allegations regarding a POSA’s motivation to combine the relied upon references and reasonable expectation of success in arriving at the claimed invention.

65. For instance, *first*, as discussed further below in Section X.A, for Grounds II and VII challenging claims 11, 39, 60–62, and 65–67 (“the Single Dose/Prime Administration Claims”), Dr. Guirakhoo fails to identify where the claimed seroconversion rates in humans are in the prior art. When Dr. Guirakhoo seeks to allege that the claimed seroconversion rates in human subjects would have

been routinely achieved by a POSA in view of Thomas, he incorrectly interprets the disclosures of Thomas as providing that the claimed seroconversion rates in human subject allegedly could be achieved after a single dose or prime administration. Such a disclosure, however, is not found in Thomas, nor would a POSA have expected to arrive at such a method in view of Thomas and the art. Indeed, while Thomas showed that single-dose vaccination may be protective in mice, a POSA would have understood that responses in mice are often not predictive of responses in humans (*see* Section X.A.2.a, below). Thomas in fact reports that a single-dose vaccination of human subjects with Thomas's vaccine did not result in significant seroconversion of the population receiving the vaccine, which was not emphasized by Dr. Guirakhoo. *See* Section X.A.1.

66. Dr. Guirakhoo also fails to cite any supporting evidence when alleging that a POSA would have reasonably expected to arrive at the claimed methods by routine optimization. Instead, Dr. Guirakhoo makes conclusory claims that a POSA would have had a reasonable expectation of success by modifying the amount of antigen and/or adjuvant and type of adjuvant in Thomas's ZIKV vaccine to achieve a seroconversion rate of at least 60% in human subjects after a single dose or prime administration. Not only does Dr. Guirakhoo fail to cite to any evidence that supports his argument, but Dr. Guirakhoo also fails to take into account that (1) the Thomas ZIKV vaccine *required two doses* to achieve the

claimed seroconversion rate and immunogenicity in human subjects; (2) the well-known characteristics of inactivated flavivirus vaccines, such as inactivated YFV, JEV, TBEV, and DENV vaccines, as requiring more than one dose to provide sufficient seroconversion in a population of human subjects; and (3) a post-filing ZIKV vaccine Phase 1 trial by Valneva, which directly contradicts his assertion.

67. *Second*, as discussed further in Section XI, Dr. Guirakhoo fails to establish why a POSA would have allegedly chosen Thomas's inactivated ZIKV vaccine to arrive at the Fetal Protection Claims (claims 9, 32–58, and 64–67) challenged in Grounds VII–XI or why a POSA would have had a reasonable expectation of success in doing so. A POSA would have been aware of the potentially fatal dangers that ZIKV poses to fetuses. A POSA would have, therefore, understood that quickly inducing a significant seroconversion rate, and with as few administrations as possible, in pregnant women would have been important. But, Thomas's vaccine achieved an insufficient titer in humans after the first dose. Thus, a POSA would not have selected Thomas's vaccine for rapid onset of immunity during pregnancy.

68. *Third*, Dr. Guirakhoo also relies on hindsight to allege that a POSA would have combined Thomas with secondary references to arrive at the Fetal Protection Claims that recite administering a 10 µg dose and/or using a vaccine comprising 200 µg adjuvant. Dr. Guirakhoo fails to support his contentions that a

POSA would have allegedly optimized the antigen dosage, adjuvant amount, and/or adjuvant type to arrive at the claimed dose and adjuvant amount. The available knowledge and prior art before November 3, 2017 establish that a POSA would not have been directed to use the claimed dose and adjuvant amount to arrive at the claimed methods. Dr. Guirakhoo, therefore, relies on hindsight and merely sought out references that disclosed the claimed dose and adjuvant amount.

69. *Lastly*, as discussed further in Section XI.B, Dr. Guirakhoo fails to establish why a POSA would have arrived at the claimed methods recited in the Fetal Protection Claims with a reasonable expectation of success. Those claims recite transferring a vaccine effective amount of neutralizing antibodies from a vaccinated pregnant human to a fetus across the placental barrier. Dr. Guirakhoo, relies on Thomas's disclosures regarding laboratory studies investigating the protective efficacy of transferring purified antibodies from one vaccinated adult animal or human to a second unvaccinated adult animal by intravenous administration, which is an experimental protocol specifically designed to study immune correlates of protection in the laboratory and not to model maternal-to-fetal transmission of antibodies. Thomas's adoptive transfer study is a fundamentally and biologically different process than the maternal transfer of antibodies across the placenta to a fetus in humans. The adoptive transfer study,

therefore, would not have informed a POSA, with a reasonable expectation of success, to arrive at the claimed methods recited in the Fetal Protection Claims.

X. GROUND II AND VII FAIL TO ESTABLISH THAT THE SINGLE DOSE/PRIME ADMINISTRATION CLAIMS WOULD HAVE BEEN OBVIOUS

A. Dr. Guirakhoo Fails To Show Where The Claimed Seroconversion Rates Are In The Prior Art And Bases His Contentions On Conclusory Statements That Lack Evidentiary Support.

70. The Single Dose/Prime Administration Claims (claims 11, 60–62, and 65–67) require achieving various rates of seroconversion of at least 60% or greater after a single dose or prime administration, i.e., after a single injection, of an inactivated ZIKV vaccine or immunogenic composition. EX1001, 123:40–52, 125:25–29, 127:23–128:9; 128:13–27.

71. The recited seroconversion rates, however, are not found in the asserted art. Dr. Guirakhoo, therefore, alleges that a POSA could have achieved the claimed seroconversion rates through routine optimization of Thomas's inactivated ZIKV vaccine. EX1002, ¶¶178, 185, 192, 200. Dr. Guirakhoo, however, fails to show that the claimed seroconversion rates would have been reasonably expected to be successfully achieved by adjusting the dose or adjuvant of Thomas's vaccine based on the prior art. In fact, data from Martinez (*see* Table in ¶54, above (citing EX2010)) and Valneva's own study with its ZIKV vaccine demonstrate that adjusting doses did not result in seroconversion of a population of human subjects

at the claimed rate. *See* Section X.C.2. And Dr. Guirakhoo fails to cite anything that supports his conclusory statements and demonstrates that a POSA could routinely optimize the dose and adjuvant of Thomas's vaccine to allegedly achieve the claimed seroconversion rates in a population of human subjects. EX1002, ¶¶177–178, 185, 192, 199. Lastly, Dr. Guirakhoo fails to take into account (1) the well-known characteristics of inactivated flavivirus vaccines as requiring more than one dose to provide sufficient seroconversion in humans; and (2) a post-filing ZIKV vaccine Phase 1 trial by Valneva, which directly contradicts his assertion.

1. Dr. Guirakhoo fails to demonstrate that the claimed seroconversion rates after a single or prime dose in a population of human subjects are disclosed in the prior art.

72. Claim 11 recites:

A method of vaccinating against Zika virus infection in a human subject in need thereof,

the method comprising administering to the human subject a vaccine or immunogenic composition comprising a dose of from about 1 µg to about 40 µg of an antigen from a Zika virus, wherein the antigen is an inactivated whole virus, wherein the vaccine or immunogenic composition is administered one or more times, wherein administration of the vaccine or immunogenic composition induces 14 and/or 28 days after a single dose or prime administration a seroconversion rate of at least 60% in a population of at least 20 Zika virus seronegative subjects.

EX1001, 123:40–52. Claim 11, therefore, requires achieving a seroconversion rate of at least 60% in a population of at least 20 Zika virus seronegative human subjects after a single dose or prime administration of an inactivated ZIKV vaccine.

73. Claims 60–62 depend from claim 11 and require seroconversion rates of at least 80%, 90%, and 95% in a population of human subjects, respectively, after a single dose or prime administration. EX1001, 127:24–128:10. Claims 39 and 65–67 also require inducing a seroconversion rate of at least 60%, 70%, 80%, and 90%, respectively, after a single dose or prime administration. EX1001, 125:25–29, 128:11–26.

74. Dr. Guirakhoo fails to identify the claimed seroconversion rates of at least 60% (claims 11 and 39), at least 70% (claim 65), at least 80% (claims 60 and 66), at least 90% (claims 61 and 67), and at least 95% (claim 62) after a single dose or prime administration in a population of human subjects in the prior art.

75. In fact, Thomas (EX1004), the primary reference that Dr. Guirakhoo relies on, did not describe a sufficient immune response in human subjects, as measured using neutralizing antibody titers, after a single dose. EX1004, 42:4–20. Thomas determined the cutoff for determining seroconversion as being a neutralizing antibody titer of 1:10. EX1004, 41:30–31. Thomas provided the

neutralizing antibody titers, reported as geometric mean titers (GMTs)⁶ in a table in Thomas’s Example 5. EX1004, 42:4–20. Thomas administered its inactivated ZIKV vaccine to human subjects at Day 0 and Day 28, which correspond to “Day 1” and “Day 29”, respectively, in Thomas’s table. EX1004, 42:4–20.

76. I have reproduced Thomas’s table below with a box outlining the antibody titer results at Day 15 and Day 29 (i.e., 14 days and 28 days after the first dose, respectively, and before administration of the second dose):

		5 mcg ZPIV				Placebo
Time Point ^a	Statistic	16-0033 (N=25)	16-0062 (N=20)	Z0001 (N=10)	All (N=55)	All (N=12)
Day 1	N*	25	20	10	55	12
	GMT	5.0	5.0	5.0	5.0	5.0
	95% CI	-	-	-	-	-
Day 15	N*	25	-	10	35	7
	GMT	5.0	-	8.6	5.8	5.0
	95% CI	-	-	2.5, 28.8	4.3, 8.0	-
Day 29	N*	25	20	10	55	12
	GMT	5.5	8.5	8.7	7.0	5.0
	95% CI	4.5, 6.8	4.7, 15.3	2.5, 30.4	5.2, 9.5	-
Day 43	N*	25	-	10	35	7
	GMT	316.9	-	983.3	437.9	5.0
	95% CI	152.9, 656.6	-	425.4, 2272.5	245.7, 780.6	-
Day 57	N*	25	17	9	51	12
	GMT	142.9	100.8	820.6	173.1	5.0
	95% CI	70.3, 290.4	39.7, 255.7	357.1, 1885.8	104.6, 286.5	-
Peak Titer	N*	25	20	10	55	12
	GMT	345.6	64.2	1061.7	229.8	5.0
	95% CI	166.4, 718.0	25.3, 163.2	452.8, 2489.2	132.6, 398.4	-

EX1004, 42:4–20 (annotated).

⁶ A geometric mean is the arithmetic mean of values taken on a log scale and is appropriately used when values change exponentially, such as when using serological dilutions. EX2023, 141.

77. Thomas observed that none of the three groups (16-0033, 16-0062, and Z0001) of human subjects achieved mean titers (“GMT”; arrows) greater than 1:10 after a single dose or prime administration of Thomas’s inactivated ZIKV vaccine. EX1004, 42:4–20.

78. Thomas reported that GMTs across the three groups (“All”) were measured to be 1:5 before vaccination on Day 1.⁷ EX1004, 42:4–20. On Day 15, i.e., 14 days, after the prime (first) administration, only one out of the three groups reported an increase of GMT to 1:8.6 and the GMT of all groups slightly increased to 1:5.8. EX1004, 42:4–20. Thomas’s inactivated ZIKV vaccine, therefore, induced mean titers of 1:5.8 (below 1:10) across all three study group populations when determined on Day 15, i.e., 14 days after the prime administration. On Day 29—when the measurement was taken 28 days after the first dose of Thomas’s vaccine and *before* the administration of the *second dose*—the GMT of all groups increased to 1:7, still below Thomas’s 1:10 cut-off value. EX1004, 42:4–20. In fact, Thomas acknowledged that “after the first dose of vaccine [] mean titers remain[ed] below the 1:10 titer cutoff.” EX1004, 42:4–20. Thomas’s

⁷ Thomas reports his GMT values using the integer value of the right hand side of the neutralizing antibody titer ratio, e.g. a GMT of 5.8 in Thomas is a ratio of 1:5.8.

vaccine, therefore, did not result in mean titers above the seroconversion cut-off of 1:10 in the population of the study's subjects after a single dose or prime administration.

79. Thomas did not observe GMT greater than 1:10 (Thomas's seroconversion cut-off) until Day 43, which is 14 days after Thomas gave the *second* (boost) administration of its inactivated ZIKV vaccine. EX1004, 42:4–20. Thomas's inactivated ZIKV vaccine, therefore, required two doses to seroconvert greater than 60% of the population of human subjects administered the vaccine. This is in line with the characteristics of other inactivated flavivirus vaccines, as discussed above in Section VIII.B.

80. Dr. Guirakhoo does not address how that data obtained with Thomas's inactivated ZIKV vaccine in human subjects impacts his analysis with respect to the Single Dose/Prime Administration Claims or otherwise point to where the claimed seroconversion rates in a population of human subjects can be found in the prior art.

2. Dr. Guirakhoo incorrectly relies on Thomas's seroprotection data from mice, which a POSA would have understood would often not predict a response in human subjects.

81. Because Thomas fails to disclose, teach, or suggest that claimed seroconversion rates in a population of human subjects after a single dose or prime administration, Dr. Guirakhoo attempts to rely on Thomas's statement that “a

single immunization of the vaccine can be shown to provide 100% complete protection in susceptible mammals against challenge with ZIKV,” which are data observed in mice, but not humans. EX1002, ¶176 (citing EX1004, 4:15–22).

a. Immune response data from mouse studies are often not predicative of human immune responses.

82. Thomas only shows that a single dose of Thomas’s vaccine induced protective antibody titers in mice, not humans. EX1004, 12:14–33, 13:1-21, 32:20-32, 33:1-4, FIG. 7a and b, FIG. 8. Yet, claim 11 requires at least 60% seroconversion rate 14 and/or 28 days after a single dose administration in a population of *human subjects*. Thomas did not achieve that rate in humans after a single dose or prime administration, observing GMTs only as high as 1:8.7. EX1004, 42:4–20. Accordingly, Thomas’s data in Example 5 did not show mean antibody titers above the seroconversion cut-off after single dose administration at Study Day 15 and Study Day 29 (i.e., 14 and 28 days after the prime (first) administration, respectively, and before the boost (second) administration). EX1004, 42:4–20.

83. *A POSA would have known that immunological pre-clinical studies in mice are often not predictive of responses in humans.* EX2021, 835–836; EX2018, 5. The art reported that “mice are lousy models” and the inbred mouse strains in use “skew the regulation of the immune response.” EX2021, 835–836. The art also stated that “[w]hile rodents ... have been employed in biomedical

research and drug/vaccine development, they often do not yield reliable preclinical results that translate into effective human treatments,” because “the immune correlates of protection in nonhuman mammalian species often diverge from human responses.” EX2018, 5. Laboratory mice are substantially different from humans, since they are genetically identical, bred in captivity, typically free of pathogens and immunologic experience, and are “short-lived [and] can replicate quickly.” EX2021, 836. Humans, in contrast, are genetically diverse, exposed to pathogens throughout life, and longer-lived and, therefore, have more evolutionary investment in their individual survival, which could create material differences in immunological responses. EX2021, 836; EX2027, 183–185; EX2030, 516; EX2029, 366.

84. Moreover, vaccine experts including Dr. David Weiner and Dr. Paul Offit have stated that “[m]ice lie and monkeys exaggerate” in terms of vaccine immune responses. EX2024; EX2025. This perspective had been shared by many investigators in the vaccine field before November 3, 2017. Thus, a POSA would not have reasonably expected that immunogenicity observed with a single immunization in mice would have also been observed in humans.

- b. Thomas's data shows that, while its vaccine was seroprotective in mice after a single dose, it failed to provide significant seroconversion in a population of human subjects after a single dose.**

85. Dr. Guirakhoo's attempt to apply Thomas's statement about "100% complete protection" after a single dose to human subjects is factually incorrect and misleading. EX1002, ¶¶455, 457, 459. Thomas only observed such a result in mice and not in humans. EX1004, 13:1–21, 32:20–32, 33:1–4. In fact, the mean titers Thomas observed in humans remained below Thomas's seroconversion cut-off of 1:10 after a single dose. EX1004, 42:4–20; *see also* ¶¶78–79, above.

86. The studies in mice from Thomas exemplify the concerns in the art about mice often not being predicative of human immunological responses. Thomas injected a single 1 µg dose of Thomas's inactivated ZIKV vaccine to Balb/c mice, which are genetically identical and highly inbred. EX1004, 32:20–26; EX2021, 835–836. Such inbreeding "creates a wealth of homozygous recessive defects that skew the regulation of the immune response." EX2021, 835–836.

87. The Balb/c mice's habitat could also have material effects on mice's immune responses that are not predicative of human immunological responses. Thomas's Balb/c mice, as with any lab-dwelling cage animals, typically would not have been exposed to any pathogens before the administration of Thomas's inactivated ZIKV vaccine. EX2027, 181. A POSA would have understood that

once exposed to antigens, the pathogen-naïve Balb/c mice can produce exaggerated immune responses. EX2027, 183–185; 2030, 516; EX2029, 366.

88. The 1 μg dosage used in Thomas is also very high in comparison with the human dose on a per weight basis, given that the weight of a typical Balb/c mouse at 6-8 weeks of age is approximately 25 g. EX2039. This comes out to a dose per weight of about 40 $\mu\text{g}/\text{kg}$.⁸ In comparison, an average human weighs 70–80 kg; the 5 μg dose injected into Thomas’s Balb/c mice, therefore, equates to about 0.0625–0.071 $\mu\text{g}/\text{kg}$.⁹ EX2034, Table 3. That is about 563-fold to about 640-fold higher of a dose compared to the human subjects on a per weight basis. To achieve this dose per weight in human subjects, Thomas would have had to administer an equivalent dose of 2,800–3,200 μg to his human subjects. Such a single dose of a vaccine would not be feasible in terms of manufacturing or dosing, and practically the maximum single dose tested in humans in Thomas was 5 μg , which is in line with doses for other inactivated flavivirus vaccines. *See, e.g.*, EX1004 42:4–20; EX2010, Table 3; EX2015, Table 2; EX2016, 20; EX2017, 1471–1472.

⁸ 1 $\mu\text{g}/25 \text{ g} = 40 \mu\text{g}/\text{kg}$.

⁹ 5 $\mu\text{g}/70 \text{ kg} = 0.071 \mu\text{g}/\text{kg}$; 5 $\mu\text{g}/80 \text{ kg} = 0.0625 \mu\text{g}/\text{kg}$.

89. A POSA, therefore, would not have expected Thomas's mice data to extrapolate and predict the potential outcome in human subjects after a single dose. Moreover, Thomas also provides its own internal evidence about how Thomas's vaccine behaved in human subjects. EX1004, 42:4–20; *see also* ¶¶78–79, above. Dr. Guirakhoo misapplies this internal evidence. As discussed herein, Thomas's own data contradicts Dr. Guirakhoo's claim that observing protective antibody titers after a single dose of Thomas's vaccine in mice would have informed that the same could be achieved in humans after a single dose. EX1004, 42:4–20; *see also* ¶¶78–79, above. To the contrary, *the same vaccine that Thomas administered by a single dose in mice did not result in mean antibody titers above the seroconversion cut-off of 1:10 when administered by a single dose in humans, but rather required two doses to achieve this seroconversion in humans.*

90. Consequently, Dr. Guirakhoo has not demonstrated that the claimed seroconversion rate of the Single Dose/Prime Administration Claims is present in Thomas.

B. Dr. Guirakhoo Provides No Evidentiary Support For His Contentions That A POSA Would Have Had A Reasonable Expectation Of Success In Arriving At The Claimed Seroconversion Rates In Human Subjects.

91. Dr. Guirakhoo states that a POSA would have a reasonable expectation of success in “modifying the vaccine dose of Thomas” to induce the claimed seroconversion rates after a single dose or prime administration. EX1002,

¶178. To do so, Dr. Guirakhoo relies on four inaccurate and unsupported statements to conclude that a POSA would have routinely optimized the ZIKV antigen and/or adjuvant amount or type of adjuvant to achieve the claimed seroconversion rate. Dr. Guirakhoo, therefore, does not establish that optimizing the dose or adjuvant of Thomas's vaccine would have allegedly resulted in the claimed seroconversion rate in a population of human subjects.

1. Dr. Guirakhoo incorrectly argues that a single dose of 10 µg of Thomas's vaccine would have given the equivalent immune response as two doses of 5 µg given weeks apart.

92. *First*, Dr. Guirakhoo incorrectly alleges that a POSA would routinely optimize the dosage of Thomas's vaccine from 5 µg to 10 µg because Thomas gave two doses of 5 µg weeks apart. Dr. Guirakhoo incorrectly alleges that a single dose of 10 µg would be immunologically equivalent to two doses of 5 µg administered in a prime-boost regimen given weeks apart.¹⁰ EX1002, ¶¶369, 382, 516. Dr. Guirakhoo states:

One of skill would have had a reasonable expectation of successfully using a 10 µg dose because Thomas demonstrated that two 5 µg doses (a total of 10 µg) were safe and provided significant immune response

¹⁰ Although Dr. Guirakhoo makes this allegation in the context of other claims that recite administering a 10 µg dose of Thomas's vaccine, his statements are relevant to show the overall fallacy of his routine optimization allegations.

to provide protection against Zika virus. Thomas demonstrated a greater immunological response and, therefore greater protection, after a second (boost) 5 μ g dose. One of skill would have reasonably expected that *the higher 10 μ g dose would provide a similar if not greater immunological response and protection against Zika virus compared to a single 5 μ g dose or two 5 μ g doses*, because the higher antigen content of the 10 μ g dose would be expected to elicit a greater immunological response compared to a 5 μ g dose, *whether the 10 μ g dose was used as a first (prime) or a (second) boost[] or as a single dose only*.

EX1002, ¶¶369, 382, 516 (emphases added).

93. Dr. Guirakhoo's above statement is remarkable in view of Thomas's own study data with human subjects and because it contradicts well established immunologic principles in terms of what was well-known in the art about immune responses and vaccine boosting.

94. First, Thomas's inactivated ZIKV vaccines only induced negligible seroconversion in the population of human study subjects that were administered the vaccine. 1004, 42:4–20. Dr. Guirakhoo, however, states that a POSA would have reasonably expected that a single 10 μ g dose “would provide *a similar ... immunological response and protection against Zika virus compared to a single 5 μ g dose*.” EX1002, ¶¶369, 382, 516 (emphasis added). But inducing a “similar immunological response” with a single 5 μ g dose of Thomas's vaccine with a

10 µg dose would not have led to the claimed seroconversion rates in a population of human subjects, as Thomas did not achieve the claimed rates with a single 5 µg dose. 1004, 42:4–20.

95. Second, as discussed in Section VIII.A.2, the immune system takes several weeks to develop a primary immune response after a novel antigen exposure. Only after a second boost exposure does the subject's anamnestic response¹¹ generally result in a more rapid and robust immune response through a greater amount of neutralizing antibodies compared to the primary response. EX2035, 13423; EX2037, 451-452; EX2036, 448–449, 451–455.

96. In Thomas, the first 5 µg dose of Thomas's inactivated ZIKV vaccine administered to ZIKV seronegative human subjects would have mounted a primary immune response. As shown in Table 5 of Thomas, the study population showed GMT amounts of 1:5.8 after 14 days of first administration and 1:7 after 28 days of first administration. EX1004, 42:4–20. The corresponding GMTs were both below the imposed 1:10 GMT cut-off value for seroconversion. EX1004, 42:4–20.

¹¹ As discussed above in ¶¶51, the “anamnestic response” is the result of the body's immune system encountering a given antigen anew after a first exposure and usually rapidly generating greater amounts of neutralizing antibodies against the antigen compared to the body's first encounter with the antigen.

Thomas only observed significant seroconversion across the human study population, greater than 88%, 28 days after administering a second 5 µg dose. The significant increase in seroconversion would have been understood by a POSA to be because of the study subjects' anamnestic response. EX1004, 42:4–20; EX2037, 451; EX2035, 13420.

97. Accordingly, a POSA would have understood that the immune response Thomas observed after two 5 µg doses with its inactivated ZIKV vaccine does not correlate to the response that would have been seen from a first, single 10 µg dose of Thomas's vaccine.

98. Dr. Guirakhoo's contention of optimizing two doses of 5 µg of Thomas's inactivated ZIKV vaccine into one dose of 10 µg, therefore, is contradicted by established basic immunology and was not observed with Thomas's inactivated ZIKV vaccine. A POSA, knowing that, would not have sought to equate the immune response of two 5 µg doses of Thomas's inactivated ZIKV vaccine given weeks apart to that of an immune response of a single 10 µg dose of Thomas's inactivated ZIKV vaccine.

2. Dr. Guirakhoo incorrectly relies on Thomas's mouse data which were not predictive of responses in a population of human subjects.

99. *Second*, Dr. Guirakhoo incorrectly applies Thomas's data from mice to humans to allege that "a single immunization of the vaccine can be shown to

provide 100% complete protection in susceptible mammals against challenge with ZIKV” and a single dose is effective and safe. EX1002 ¶178; EX1004 4:15–22, 18:17–20. But, as discussed in Section X.A.2, immune responses in inbred laboratory mice are often not predictive of human immune responses; often, inbred laboratory mice overestimate human immune responses. EX2021, 835–836; EX2018, 5. The Single Dose/Prime Administration Claims require achieving the claimed seroconversion rates after a single dose in *human subjects*. EX1001, 123:40–52. Thomas’s own data shows that Thomas did not achieve that rate in a population of human subjects after a single dose or prime administration. EX1004, 42:4–20.

100. Additionally, while vaccines are typically administered as constant doses to humans, it is worth noting that the dose Thomas administered to its inbred Balb/c mice was far higher on a per weight basis than what Thomas administered (or could have administered) to human subjects. *See* ¶88, above. The immune response induced by Thomas’s vaccine in those pathogen-naïve, inbred mice, therefore, would not have been expected to correlate to an adult human response, especially where Thomas’s adult humans have previously been exposed to numerous pathogens and were administered a 600-fold lower dose per weight. EX2027, 183–185; EX2029, 366; EX2030. Thomas, moreover, did not achieve the

claimed seroconversion rates after a single dose in its human study subjects.

EX1004, 42:4–20.

101. Dr. Guirakhoo, thus, incorrectly applies Thomas’s statement based on mouse data to what he alleges would have happened in humans.

3. Thomas’s statement regarding exploring a range of antigen doses does not support Dr. Guirakhoo’s conclusory claim.

102. *Third*, Dr. Guirakhoo relies on Thomas’s statement that “ZPIV [sic] is explored across a range of antigen doses.” EX1002, ¶124; EX 1004 40:19-21. But this is also misplaced in supporting that a POSA could have achieved the claimed seroconversion rates in human subjects after a single dose or prime administration. EX1002, ¶124. As discussed above in Section VIII.B and below in Section X.C.1, inactivated flavivirus vaccines known in the art before November 3, 2017, were not sufficiently immunogenic after a single dose and failed to achieve greater than a 60% seroconversion rate in human subjects. EX2016, 20; EX2015, Table 2; EX2010, Table 3; EX2017, 1471–1472. Dr. Guirakhoo’s reliance on Thomas’s 92% seroconversion rate after two doses, moreover, would not have been indicative of the outcome after a single dose based on Thomas’s own single-dose data in humans. EX1004, 42:4–20. As discussed above in Section X.B.1, Dr. Guirakhoo also wrongly equates two 5 µg doses of Thomas’s inactivated ZIKV vaccine with a single 10 µg dose to support his argument that adjusting the dose of Thomas’s vaccine would have resulted in greater seroconversion. EX1002

¶¶465–482, 513–521. Upon receiving a second 5 µg dose, Thomas’s human study subjects had an increased immune response, i.e., the anamnestic response. *See* Section, X.B.1, above; EX1004, 42:4–20. That anamnestic response led to seroconversion in greater than 88% of the population of Thomas’s human study subjects, and it does not equate to the primary immune response that would be induced by a first, single 10 µg dose of Thomas’s inactivated ZIKV vaccine.

103. Consequently, a POSA would not read Thomas’s statement about “explor[ing] across a range of antigen doses” as providing a reasonable expectation that Thomas’s vaccine would have achieved the claimed seroconversion rates in a population of human subjects after a single dose or prime administration

4. Dr. Guirakhoo cites no evidence that establishes that the dose or adjuvant in Thomas’s vaccine is a result-effective variable.

104. *Fourth*, Dr. Guirakhoo cites no evidence to support his statement that “the amount of antigen and/or adjuvant or the type of adjuvant make the vaccine dose a result-effective variable” and “Thomas demonstrates that vaccine dose affects seroconversion after a first (prime) dose, as well as after a second (boost dose).” EX1002 ¶¶177–178, 199–200. Dr. Guirakhoo simply states,

Thomas also teaches that administering a dose of an inactivated, whole Zika virus antigen vaccine effects seroconversion of the human to whom the dose is administered. In particular, seroconversion is

increased relative to a human who has not received the vaccine dose after a first (prime) dose and after a second (boost) dose.

EX1002, ¶172. That Thomas observed a small subset of Thomas's seronegative subjects seroconvert after receiving "a dose" of Thomas's vaccine would not have been surprising to a POSA. The rate of seroconversion that Thomas observed after the first dose of Thomas's inactivated ZIKV vaccine, however, in the population of its study subjects was negligible and completely in line with other known inactivated flavivirus vaccines that did not induce significant seroconversion in a population of human subjects after a single dose. EX1004, 42:4–20; *see* Section VIII.B. Thus, Dr. Guirakhoo's statement does not establish that adjusting the dose of Thomas's vaccine would have resulted in the claimed seroconversion rates of at least 60% or greater or that a vaccine's dose is a result-effective variable in relation to comparing one dose to another dose.

105. Thomas's failure to achieve the claimed seroconversion rate of at least 60% after a single dose or prime administration in a population of human subjects, moreover, directly undermines Dr. Guirakhoo's claim that doing so would have been easily achieved by altering the dose and the amount or type of adjuvant. Indeed, Dr. Guirakhoo's allegations about simply adjusting Thomas's dose and/or adjuvant leading to the claimed seroconversion rates runs contrary to what was known about inactivated flavivirus vaccines known in the art before November 3,

2017, as discussed in Section VIII.B, above, that failed to achieve the claimed seroconversion rate in a population of human subjects after a single dose. In fact, Martinez discloses that the human subjects had the approximately the same seroconversion rates at 11% and 10% after receiving either a single 2.5 µg and 5 µg dose, respectively. EX2010, Table 3.

106. In fact, if Dr. Guirakhoo's contentions were correct, then POSAs would have successfully made most, if not all, inactivated flavivirus vaccines into single dose vaccines simply by increasing the dosage, adjuvant, and/or adjuvant type. Thomas, however, did not achieve a single-dose inactivated ZIKV vaccine. *See* Section X.A.1, above. And as discussed in Section VIII.B, above, inactivated flavivirus vaccines known in the art before November 3, 2017, required two doses to achieve at least 60% or greater seroconversion in a population of human subjects.

107. Dr. Guirakhoo, therefore, has not demonstrated that a POSA would have been able to routinely optimize Thomas's inactivated ZIKV vaccine to achieve the claimed seroconversion rate in humans, as recited in the Single Dose/Prime Administration Claims. Dr. Guirakhoo also fails to provide any citations to support a POSA's reasonable expectation of success to achieve the claimed seroconversion rates in human subjects as recited in the Single Dose/Prime Administration Claims based on Thomas and the prior art. EX1002, ¶¶178, 185,

192. The provided claim chart in Appendix B of Dr. Guirakhoo's Declaration also does not provide any additional support for the arguments made by Dr. Guirakhoo. EX1002, Appx. B. 20–22, 105–109.

C. Dr. Guirakhoo Fails To Address Other Evidence That Contradicts His Conclusory Opinions.

108. In addition to not showing where Thomas discloses the claimed seroconversion rates of the Single Dose/Prime Administration Claims, Dr. Guirakhoo fails to address that before November 3, 2017, inactivated flavivirus vaccines in the art required at least two doses to achieve significant seroconversion in a population of human subjects. Valneva's own Phase 1 trial of its inactivated ZIKV vaccine also contradicts Dr. Guirakhoo's claim that a POSA could have routinely optimize an inactivated ZIKV vaccine to achieve the claimed seroconversion rates of the Single Dose/Prime Administration Claims. *See* EX2007, 6.

1. Dr. Guirakhoo fails to address that inactivated flavivirus vaccines known in the prior art required more than one administration to confer seroconversion rates in a population of human subjects as claimed.

109. As discussed previously in Section VIII.B, it was well known that the dosing regimens for inactivated flavivirus vaccines known in the art required more than one administration in humans to result in the claimed seroconversion rate of at

least 60%. Dr. Guirakhoo fails to address this fact that would have been well-known to a POSA.

110. As discussed in Section VIII.B, the inactivated YFV vaccine, XRX-001, required a two-dose administration schedule. XRX-001 failed to reach 50% seroconversion in humans, reaching a seroconversion rate of only 32%. EX2015, Table 2. Valneva's inactivated JEV vaccine, IXIARO[®], provided a seroconversion rate of about 40% in humans after the first administration. EX2016, 20. Martinez's inactivated DENV serotype 1 vaccine provided a seroconversion rate of only 11% and 10% after one administration at two different doses (2.5 µg and 5 µg, respectively), contrary Dr. Guirkahoo's claim that adjusting the dose could affect seroconversion rates. EX2010, Table 3. And the inactivated TBEV vaccine, Encepur[®], again provided 28% or 29% seroconversion rate in humans after the first dose. EX2017, 1471–1472.

111. From that, a POSA would have known that inactivated whole flavivirus vaccines in the art before November 3, 2017 and discussed herein were not single-dose administration vaccines. A POSA, moreover, would have known about the seroconversion rates in humans of inactivated YFV, TBEV, JEV, and DENV flavivirus vaccines after a single dose. In fact, Thomas refers to “information known about the dosing and schedule for other [purified, inactivated] flavivirus vaccines – such as Japanese encephalitis and tick-borne encephalitis”

that would have informed someone skilled in the art about a potential dosing schedule for Thomas's inactivated ZIKV vaccine. EX1004, 4:24–28. Dr. Guirakhoo, however, curiously fails to acknowledge this information, which a POSA would have considered when analyzing the claimed methods. Dr. Guirakhoo also fails to identify any inactivated flavivirus vaccines with single-dose administration schedules for humans in his Declaration. Dr. Guirakhoo overlooks this information, which further renders weak the merits of Dr. Guirakhoo's contentions.

112. In view of ¶¶70–107, above, Dr. Guirakhoo fails to establish that an inactivated flavivirus vaccine or composition that induces a seroconversion rate of at least 60% 14 and/or 28 days after a single dose or prime administration was present in the prior art or that a POSA would have had a reasonable expectation of success in achieving the claimed seroconversion rates with an inactivated ZIKV vaccine before November 3, 2017. Therefore, Dr. Guirakhoo has not established that this element of claims 11 and 39 is present in the prior art or that a POSA would have arrived at it with a reasonable expectation of success. Accordingly, Dr. Guirakhoo also fails to show that the seroconversion rates recited in claims 60–62 and 65–67, which are even higher, are also in the prior art or that a POSA would have arrived at them with a reasonable expectation of success.

2. Valneva’s own clinical trial data contradicts Dr. Guirakhoo’s unsupported conclusions regarding routine optimization.

113. Valneva’s own Phase 1 trial of its inactivated ZIKV vaccine also does not reflect Dr. Guirakhoo’s contention that a POSA would have had a reasonable expectation of success to achieve at least 60% seroconversion rate after a single dose. On multiple occasions, Dr. Guirakhoo states that a POSA would have achieved the claimed seroconversion rates “from routine optimization of the amount of antigen and/or adjuvant or the type of adjuvant in the vaccine dose based on Thomas teaching.” EX1002, ¶¶178, 185, 192, 200.

114. In a post-filing Phase 1 trial conducted in 2018, Valneva (the Petitioner) evaluated two doses (3 antigen units (3AU) and 6 antigen units (6AU)) of its inactivated ZIKV vaccine using two different dosing regimens (“standard” and “rapid”) and reported the results in 2022 in Wressnigg et al. EX2007. Valneva developed this vaccine candidate on the same platform as the one it used for IXIARO[®] (discussed above), which is a vaccine against JEV (another closely related member of ZIKV in the *Flaviviridae* family). EX2007, 1.

115. Valneva’s studies with its own inactivated ZIKV vaccine contradict Dr. Guirakhoo’s claims that a POSA could simply optimize a given vaccine to achieve the claimed seroconversion rates. Wressnigg’s data shows that in adjusting the dose (3AU vs. 6 AU) and dosing schedule (vaccination on Days 0 and 28 for

the “standard regimen” vs. vaccination on Days 0 and 7 for the “rapid regimen”), Valneva was still not able to achieve the claimed seroconversion rates after a single dose. EX2007, 6.

116. Figure 2 in Wressnigg shows that Valneva did not observe at least 60% seroconversion in the study subjects until after two doses or not at all. EX2007, 6, FIG. 2. Figure 2 shows that (1) both the 3AU and 6AU in the “standard regimen” schedules did not achieve at least 60% seroconversion rate until after the second dose (i.e., on Day 35), and (2) the 6AU “rapid regimen” schedule did not induce at least 60% seroconversion until after the second dose, i.e., at Day 28; and (3) the 3AU “rapid regimen” schedule never induced at least 60% seroconversion, even after two doses. EX2007, 6, FIG. 2.

117. Contrary to Dr. Guirakhoo’s conclusory argument, therefore, an adjusting of doses (3AU and 6AU), as well as the adjusting of dosing schedules, failed to achieve successful seroconversion rate of at least 60% after a single dose of Valneva’s inactivated ZIKV vaccine in human subjects.

XI. GROUNDS VII–XI FAIL TO ESTABLISH UNPATENTABILITY OF THE FETAL PROTECTION CLAIMS

A. Dr. Guirakhoo Fails to Establish Why A POSA Would Have Combined The Prior Art And Sought To Practice The Claims.

118. The Table below shows prior art that Dr. Guirakhoo seeks to combine in Grounds VII-XI.

Ground	Prior Art
Ground VII	Thomas, Faucette
Ground VIII	Thomas, Faucette, NCT02952833
Ground IX	Thomas, Faucette, Barbero
Ground X	Thomas, Faucette, NCT02952833, Barbero
Ground XI	Thomas, Faucette, Murata

119. By proposing five different combinations of prior art that do not appear to build on each other, Dr. Guirakhoo essentially proposes that a POSA would seek five different pathways to arrive at the invention claimed in the '802 Patent. And in making his proposed combinations, Dr. Guirakhoo's analysis indicates that he has just sought out where the elements of the challenged claims were found in the applied references. Indeed, Dr. Guirakhoo generally does not specify why a POSA would choose certain elements of the claims of the '802 patent challenged in Grounds VII–XI and practice them in the claims as a whole, as discussed in the sections below.

1. Dr. Guirakhoo fails to establish why a POSA would have sought to practice the fetal protection claims with Thomas’s inactivated ZIKV vaccine.

120. Grounds VII–XI all rely on Thomas and Faucette, along with combinations of NCT02952833, Murata, and Barbero. EX1002, ¶4. Each of the Fetal Protection Claims (claims 9, 32–58, and 64–67) challenged in Grounds VII–XI requires “transfer[ing] a vaccine effective amount of neutralizing antibodies against Zika virus *to the fetus or newborn*.” EX1001, 123:24–34, 124:62–127:19, 128:12–27 (emphasis added).

121. To address the Fetal Protection Claims, Dr. Guirakhoo seeks to combine Thomas with Faucette. He states that Thomas teaches a need to protect both the pregnant woman and the fetus from a ZIKV infection, and Faucette teaches that immunizing pregnant women “can generate maternal immune protection as well as elicit the production and transfer of antibodies cross the placenta... to provide early infant protection.” EX1002, ¶418 (citing EX1007 Abstract, 2549; EX1004 2:13–24, 4:2–7, 18:26–30).

122. Dr. Guirakhoo, however, does not explain why a POSA would seek to use Thomas’s vaccine that required two doses, administered 28 days apart, to effectuate significant seroconversion in a population of human subjects in an effort to transfer a vaccine effective amount of neutralizing antibodies against Zika virus *to the fetus or newborn*. In fact, as discussed in Section VIII.C, it was known in the

art that ZIKV infection during pregnancy can have fatal outcomes (such as congenital defects) in fetuses. EX2020, 1982. Thus, a POSA seeking to protect a fetus via transfer of maternal antibodies would have understood that quickly inducing a significant seroconversion rate, and with as few administrations as possible, in pregnant women would have been important. It would have been undesirable to have to wait several weeks to give a second dose or further doses to confer a sufficient immune response supporting protection, but Thomas's vaccine achieved a geometric mean titer of 1:7 28 days after the first dose in humans (below Thomas's 1:10 cut-off value), which a POSA would have expected to be insufficient. EX1004, 42:4-20 ("All" groups). Thus, a POSA would not have selected Thomas's vaccine for rapid onset of immunity during pregnancy.

123. As discussed above in Section X.B, Thomas's ZIKV vaccine, moreover, would not have been reasonably expected to be routinely optimized to achieve seroconversion with a single dose or prime administration.

124. First, Thomas's statement that "a single immunization of the vaccine can be shown to provide 100% complete protection in susceptible mammals against challenge with ZIKV" is misleading because this statement was based on mice data, which is often not predictive of immune responses in humans. Thomas's own data showed that a "single immunization of the vaccine" worked in mice, but not in humans. EX1004, 42:9–20. A POSA, therefore, would not have relied on

Thomas's teachings that a single dose can "provide 100% protection in susceptible mammals against challenge with ZIKV."

125. Second, a POSA would have understood that a single dose of 10 μ g will not induce the similar immune response as two 5 μ g doses of Thomas's inactivated ZIKV vaccine due to the lack of the anamnestic response. A POSA, therefore, would not have expected to achieve the claimed seroconversion rates from changing two 5 μ g doses of Thomas's inactivated ZIKV vaccine given weeks apart to a single 10 μ g dose of Thomas's inactivated ZIKV vaccine. *See* Section X.B.1, above. Put another way, a POSA would not have expected a single 10 μ g dose of Thomas's inactivated ZIKV vaccine to induce a similar, let alone a higher, seroconversion rate than that observed with two 5 μ g doses administered several weeks apart. *See* Section X.B.1, above.

126. Third, as discussed in Section VIII.B, known inactivated flavivirus vaccines before November 3, 2017, required at least two doses to induce at least a 60% seroconversion rate in human subjects. EX2016, 20; EX2015, 1331; EX2010, Table 3; EX2017, 1471–1472.

127. Finally, as discussed in Section X.B, Dr. Guirakhoo fails to cite any evidence that supports that a POSA could have changed the dose amount, adjuvant amount, and/or adjuvant type of Thomas's ZIKV vaccine to achieve the claimed seroconversion rate. Martinez's inactivated DENV-1 vaccine and Valneva's own

inactivated ZIKV vaccine that were each administered at different doses and each failed to achieve the claimed seroconversion rates also contradict Dr. Guirakhoo's claims. *See* Section X.C, above.

2. Dr. Guirakhoo does not establish why a POSA would have combined Thomas, Faucette, and NCT02952833 in Grounds VIII and X to arrive at the claimed 10 µg dose.

128. In Grounds VIII and X, Dr. Guirakhoo seeks to combine Thomas, Faucette, and NCT02952833. EX1002, ¶¶465–482, 513–521. Dr. Guirakhoo inaccurately alleges that a POSA would have been motivated to adjust the dosage of Thomas's ZIKV vaccine to 10 µg because the dosage would have been a result-effective variable affecting seroconversion rate. EX1002, ¶470. As discussed above in Section X.B.1, however, this conclusion goes unsupported by Dr. Guirakhoo and is based on his inaccurate understanding of Thomas.

129. Dr. Guirakhoo also identifies no reason to combine NCT02952833 with Thomas and Faucette, other than the hindsight-based reason to that NCT02952833 discloses claimed 10 µg dose recited in Claims 34, 37, 40, 42–46, 48, 50, and 52. EX1002, ¶¶465–482, 513–521. In fact, Dr. Guirakhoo's only bases for selecting a 10 µg dose are Thomas's statement that other inactivated flavivirus vaccine doses could purportedly be informative for a ZIKV vaccine and purportedly a range of doses should be explored. EX1002, ¶470. That reliance, however, is not based on any evidence on how the claimed 10 µg dose would have

been expected to function in view of the whole claim. In other words, Dr. Guirakhoo does not explain how a POSA would have reasonably expected the claimed 10 µg dose to lead to the claimed fetal protection through transfer of a vaccine effective amount of neutralizing antibodies from a vaccinated subject to their fetus. EX1002, ¶470.

130. Dr. Guirakhoo incorrectly alleges that a POSA would have been informed when looking to NCT02952833 for selecting a dose for pregnant women. EX1002, ¶467. Dr. Guirakhoo states that a POSA “would have looked to the art for examples of [ZIKV purified-inactivated virus] doses for use with women, and further for use with pregnant women, as a matter of routine skill and would have been aware of Version 8 of NCT02952833.” EX1002, ¶467. But pregnant women were specifically excluded from the NCT02952833 study. The study’s inclusion criteria states,

Women of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test immediately prior to each vaccination.... Women of childbearing potential must use an acceptable method of contraception from one month (30 days) prior to the first vaccination until at least 60 days after the last vaccination.

EX1011, 12. NCT02952833, therefore, does not indicate that a 10 µg dose would be appropriate for pregnant women.

131. Dr. Guirakhoo wrongly relies on his unsupported contention that the claim dose of 10 μg is a result-effective variable affecting seroconversion, which could have been routinely optimized. As discussed above in Section X.B.1, this contention is misplaced and unsupported by the prior art.

132. Dr. Guirakhoo, therefore, solely relies on NCT02952833's disclosure of the claimed 10 μg dose as recited in Claims 34, 43–46, 48, 54, and 64 as a basis for combining NCT02952833 with Thomas and Faucette. Indeed, Dr. Guirakhoo's only support for selecting a 10 μg dose for pregnant subjects is Thomas's statement that other flavivirus vaccine doses could be informative and a range of doses should be explored, but not based on any evidence on how the claimed 10 μg dose would have been expected to function in view of the whole claim. EX1002, ¶470.

133. Dr. Guirakhoo does not cite to any prior art to support his claim that adjusting the inactivated ZIKV vaccine's dose would have seroconverted subjects after a single dose. In fact, Martinez investigated a 2.5 μg and 5 μg dose of its inactivated DENV-1 vaccine in humans and did not see any difference in the seroconversion rates after a single dose. EX2010, Table 3. Valneva's study with its own inactivated ZIKV vaccine also demonstrates that adjusting the dose did not result in sufficient seroconversion after a single dose. EX2007, 2, FIG. 2. Consequently, a POSA would still not have selected Thomas's inactivated ZIKV

vaccine to vaccinate pregnant subjects because the POSA would not have expected that simply adjusting the dose of Thomas's inactivated ZIKV vaccine would have resulted in sufficient seroconversion in a population of human subjects after a single dose. Dr. Guirakhoo, moreover, does not explain how adjusting the dose of Thomas's vaccine to 10 µg would have reasonably been expected to lead to the claimed fetal protection through transfer of a vaccine effective amount of neutralizing antibodies from a vaccinated pregnant human subject to her fetus. EX1002, ¶¶470–471.

3. Dr. Guirakhoo does not establish why a POSA would have combined Thomas, Faucette, and Barbero in Ground X to arrive at the claimed amount of adjuvant.

134. Dr. Guirakhoo fails to establish a POSA's motivation to combine Thomas, Faucette, and Barbero in Ground X. EX1002, ¶¶513–521.

135. Dr. Guirakhoo states that Barbero teaches 500 µg of an aluminum hydroxide adjuvant per ml of ZIKV vaccine. Then, Dr. Guirakhoo states:

A POSA would have been motivated to modify the 500 µg amount of the aluminum hydroxide adjuvant of Barbero to 200 µg because Thomas teaches to use a suitable amount of an adjuvant. The amount of adjuvant is a routine design parameter for vaccines and is a result-effective variable affecting seroconversion. One of skill would have been able to modify the 500 µg to 200 µg as a matter of routine optimization using ordinary skill, simply by lowering the amount of adjuvant combined with the inactivated whole Zika virus antigen.

EX1002, ¶517. However, Dr. Guirakhoo does not explain or support with evidence why he chooses 200 µg as a “suitable amount of adjuvant.” Rather, Dr. Guirakhoo makes a conclusory statement to support his contention that a POSA would have been motivated to choose a specific dependent claim element, such as 200 µg aluminum hydroxide adjuvant because it is allegedly a “result-effective variable affecting seroconversion.” EX1002, ¶517. As discussed above in Section X.B.4, however, this conclusion goes unsupported by Dr. Guirakhoo and does not establish that adjusting the dose or adjuvant can affect seroconversion rates in a population of human subjects with an inactivated ZIKV vaccine.

136. A POSA would not have arrived at the claimed 200 µg of adjuvant from the teachings of Thomas and Barbero. Dr. Guirakhoo argues that since Thomas discloses using a “suitable amount of adjuvant,” a 200 µg amount would have been a “suitable amount of adjuvant” without citing any support. Dr. Guirakhoo thereby seeks to lower the adjuvant amount of 500 µg disclosed in Barbero to 200 µg, as claimed in the ’802 patent to arrive at a “suitable amount of adjuvant.” EX1002, ¶517.

137. A POSA would have understood that the facts would teach away from a 200 µg adjuvant amount as a “suitable amount of adjuvant.” Thomas required two doses of its inactivated ZIKV vaccine to achieve the claimed seroconversion rate; a single dose failed to do so. EX1004, 42:9–20. A POSA, therefore, would

have sought to use a known adjuvant amount or increase a known adjuvant amount to try to increase the vaccine's effectiveness. But, as Dr. Guirakhoo plainly acknowledges, Thomas states that "[a]n 'adjuvant' is a substance that serves to *enhance, accelerate, or prolong* the antigen-specific immune response of an antigen when used in combination with specific vaccine antigens." EX1004, 28:19–21; EX1002, ¶388. Yet, Dr. Guirakhoo does not cite any evidence to support his conclusion that *decreasing* the amount of aluminum hydroxide from 500 µg, as Barbero teaches, to 200 µg would *positively* affect seroconversion rate and "result in vaccination." A POSA, therefore, would not have sought to *decrease the adjuvant amount* from Barbero's disclosed 500 µg adjuvant amount to the claimed 200 µg of adjuvant, so as to attempt to achieve a seroconversion rate of at least 60% with a single dose.

138. Consequently, it appears that Dr. Guirakhoo landed on selecting using 200 µg aluminum hydroxide adjuvant solely because the claims challenged in Ground X recite that amount of adjuvant, and not based on any evidence on how the claimed amount of aluminum hydroxide would have been expected to function in view of the whole claim. EX1002, ¶¶517–518. In other words, Dr. Guirakhoo does not explain how a POSA would have reasonably expected the claimed amount of 200 µg aluminum hydroxide adjuvant to lead to the claimed fetal

protection through transfer of a vaccine effective amount of neutralizing antibodies from a vaccinated pregnant human subject to their fetus. EX1002, ¶470.

139. In view of the above, Dr. Guirakhoo fails to establish why a POSA would have combined the prior art and seek to practice the elements of the claims challenged in each of Grounds VII–XI.

B. Dr. Guirakhoo Fails To Establish Why A POSA Would Have Had A Reasonable Expectation Of Success In Arriving At The Methods Of The Fetal Protection Claims.

140. As discussed above, each of the Fetal Protection Claims (claims 9, 32–58, and 64–67) challenged in Grounds VII–XI requires “transfer[ing] a vaccine effective amount of neutralizing antibodies against Zika virus *to the fetus or newborn.*” EX1001, 123:24–34, 124:62–127:19, 128:12–27 (emphasis added).

1. Dr. Guirakhoo incorrectly conflates lab experiments using adult animal recipients of purified antibodies with natural human mother-to-fetus transplacental transfer of unpurified antibodies.

141. Dr. Guirakhoo makes the conclusory statement that Thomas allegedly teaches a successful adoptive transfer experiment in animal studies as supporting his contention that a POSA would have been motivated to combine Thomas and Faucette to arrive at the claimed methods of transferring a vaccine effective amount of neutralizing antibodies against ZIKV virus to the fetus or newborn. EX1002, ¶¶407–411. But those studies in Thomas are laboratory experiments of **intravenous** transfer of **purified** antibodies to **adult animal recipients**; not

natural human mother-to-fetus transfer of antibodies *in utero* and across the placenta. EX1004, 38:5–16; 38:17–22; 8:24–26; 38:30–39:2. **The adoptive transfer of antibodies to adult animals in Thomas are a fundamentally different processes than maternal-to-fetal transfer.**

142. As the lead scientist who conceptualized, designed, performed, and reported the adoptive transfer studies in Thomas, I personally designed these experimental protocols to study immune correlates of protection in the laboratory, not to model maternal-to-transfer transmission of antibodies. EX2003; 2004. Thomas's adoptive transfer studies, therefore, would not be informative as to what a POSA would have reasonably expected in regard to mother-to-fetus transfer of antibodies. The table below compares the differences between these two largely unrelated processes, and I explain below how a POSA would have understood these differences.

	Experimental Adoptive Transfer of Antibodies to Adult Mice or Monkeys	<i>In Utero</i> Maternal-to-Fetal Transfer of Antibodies in Humans
Objective	Protection against experimental challenge to define immune correlates and antibody titers required for protection	Prevention of the neurologic developmental birth defects known as congenital ZIKV syndrome in the fetus
Setting	Laboratory experiment	Natural pregnancy
Donor Species	Monkey, human	Human
Donor Age	Adult	Adult
Recipient Species	Mice, monkey	Human
Recipient Age	Adult	Fetus in utero
Relationship	Unrelated	Mother
Transferred Material	Purified IgG antibodies	Unpurified antibodies with inflammatory plasma components
Antibody Route	Intravenous (IV)	Trans-placental
ZIKV Exposure	Protection against systemic experimental ZIKV challenge (SQ or IV)	Prevention of natural in utero ZIKV infection (trans-placental)
ZIKV Dose	High-dose challenge	Typical human exposure (lower dose)

a. The desired goal of the Thomas's and the mother-to-fetus transfer process are fundamentally different.

143. The objective of the adoptive transfer studies in adult animals in

Thomas was fundamentally different than the objective of mother-to-fetus transfer

of antibodies in humans. A POSA would have understood that Thomas's adult adoptive transfer study aimed to demonstrate that intravenous injection of purified antibodies, in isolation from other immune components, would protect against ZIKV challenge in naïve adult animals. EX2004, 1129–1130. Those experiments in Thomas would have been understood by a POSA to have been used by Thomas (1) to confirm that the antibodies induced by Thomas's vaccine were in fact the mechanistic correlate of protection against experimental ZIKV challenge and (2) to help define the antibody titer required for protection in this animal model through *in vitro* studies of ELISA and microneutralization assay. In contrast, the mother-to-fetus *in utero* transfer of antibodies involves the natural process of antibodies crossing the placental barrier to protect the fetus against ZIKV and the development of neurologic consequences of congenital ZIKV syndrome.

144. Congenital ZIKV syndrome involves fetal neurologic developmental birth defects as a result of in utero ZIKV infection, which is very different and far more complicated than viral replication in peripheral blood after an experimental ZIKV challenge of laboratory animals. In fact, by November 3, 2017, the art provided that fetal ZIKV infection occurred through transplacental transmission of the virus to the fetus. EX2031, 1082, 1085; EX2033, 1258. The studies also showed that the placenta was a site of preferential replication of ZIKV compared to maternal serum, and placental ZIKV infection led to placental malfunction and

placental cell death. EX2031, 1082, 1085; EX2033, 1258. Those studies also reported that ZIKV fetal infection led to cell death in fetal neural tissues and restricted fetal brain growth. EX2032, 270; EX2033, 1257. In contrast, Thomas's adoptive transfer studies set out to investigate the ability of ZIKV vaccination to simply prevent ZIKV replication in blood and had nothing to do with ZIKV neuropathology or the process of how ZIKV leads to neurologic congenital tissue damage that results in birth defects. EX2004, 1130, FIGs. 3 and 4.

145. Due to these fundamentally different mechanisms between the adoptive transfer of antibodies to adult animals and mother-to-fetus trans-placental transfer of antibodies in humans, a POSA would not have expected that the same immunologic mechanisms or protective antibody titers from the adoptive transfer studies in adult animals would be necessarily relevant for the *in utero* ZIKV infection and the congenital ZIKV syndrome. As discussed herein, Thomas's adult adoptive transfer study, thus, would not reasonably inform a POSA on fetal protection from the ZIKV virus through *in utero* mother-to-fetus antibody transfer. Those differences between the adoptive transfer mechanisms in Thomas and mother-to-fetus transfer of antibodies would have made the results from the adoptive transfer study not likely predictive of the results of the mother-to-fetus transfer.

b. Antibody dose, formulation, and route of administration are different between Thomas's adoptive transfer studies and mother-to-fetal transfer.

146. Thomas's adoptive transfer study's antibody dose, antibody formulation, and route of administration of the antibody fundamentally differ from those of the mother-to-fetus transfer. Thomas's adoptive transfer study in adult animals used purified IgG antibodies obtained from vaccinated monkeys or humans that were intravenously infused into the recipient mice and monkeys. EX1004, 33:21–28, 38:5–29, 43:5–10. Thomas purified the IgG from plasma of monkeys and humans immunized with the ZIKV vaccine, then intravenously injected the purified IgG into seronegative Balb/c mice and rhesus monkeys. EX 1004, 33:21–28, 38:5–29, 43:5–10. The purified IgG, therefore, was directly released into the peripheral bloodstream, where it could start to neutralize the ZIKV in the host's bloodstream. EX2041, 543 (stating that the antibodies developed in response to Zika virus are “[n]eutralizing antibodies”). That is fundamentally different from the naturally occurring transfer of the maternal antibodies across the placental barrier from a mother to her fetus with inflammatory proteins from the mother's plasma and with an unknown antibody titer in the fetus. EX2043, 12. The presence of inflammatory cytokines, innate mediators, and other plasma components would also have been known by a POSA as being able to modulate the functions of antibodies. EX2042, Abstract, 5;

EX2038, Abstract, 84. These major differences in the antibody dose, formulation, and route make the results of the adult adoptive transfer study in Thomas not predictive of mother-to-fetus transfer of antibodies to confer fetal protection from ZIKV.

c. ZIKV dose, formulation, and route of infection are different between Thomas's adoptive transfer studies and mother-to-fetal transfer.

147. Thomas's adoptive transfer studies involved intravenously or subcutaneously administering a high-dose ZIKV challenge to the animal recipients. EX1004, 38:5–29, 43:5–10; EX2004, 1129–30. Thomas's high-dose ZIKV challenge was not physiological in terms of the natural amount ZIKV that would typically enter a subject through a mosquito bite. EX1004, 38:5–29, 43:5–10; EX2004, 1129–30. As discussed above, moreover, Thomas investigated whether using purified IgG, directly released into the peripheral bloodstream, where it could start to neutralize the ZIKV directly in the host's bloodstream, could protect against that high dose.

148. A POSA would have understood that Thomas's experimental system would not have been informative for mother-to-fetal transfer because (1) the different pathology of fetal ZIKV infection and Thomas's studies; and (2) the ZIKV dose a fetus would receive from the placental transfer of the virus from an infected mother was unknown, as well as what immune response would be needed

to protect against that dose. EX2040, 6-7, 9. Those major differences in the ZIKV dose, format, and route of infection also make the results of Thomas's adoptive transfer studies not reasonably predictive of successful vaccine protection arising from mother-to-fetus transfer.

d. Thomas's and the mother-to-fetus processes involve different donor and recipient species.

149. The adoptive transfer study in adult animals and the mother-to-fetus transfer of antibodies across the placental barrier involve different donor and recipient species. The donor species that generated the neutralizing antibodies from the ZIKV vaccine in Thomas's intravenous adoptive transfer studies were monkeys or humans, and the recipients were adult mice or monkeys (but not humans). EX1004, 38:5–29, 43:5–9; 2004, 1129–30. As discussed above, immunological responses in mice are often not predictive of human responses. *See* Section X.A.2.a. Also, nonhuman primates (monkeys) would also have been considered by a POSA to “often [] not yield reliable preclinical results that translate into effective human treatments.” EX2018, 5. In contrast, the Fetal Protection Claims involve transferring neutralizing antibodies from a human adult to a human fetus by the trans-placental route. A POSA would have understood that the differences in recipient species, therefore, also would have made the results of Thomas's adoptive transfer studies not predictive of mother-to-fetus transfer results.

150. Accordingly, each of the differences outlined above would have led a POSA to conclude that the results of Thomas's adoptive transfer studies would not have provided a reasonable expectation of success in protecting a pregnant woman or fetus though a mother-to-fetus transfer of neutralizing antibodies. A POSA would have understood that an adult, animal adoptive transfer study of purified IgG injected intravenously is fundamentally different than preventing congenital ZIKV syndrome, including microcephaly, by mother-to-fetus transfer of neutralizing antibodies, followed by a natural *in utero* infection of the fetus.

2. Dr. Guirakhoo does not provide any evidence that a POSA would have had a reasonable expectation of achieving transfer of a vaccine effective amount of neutralizing antibodies from a human mother to the fetus.

151. Dr. Guirakhoo, moreover, does not provide any evidence that one would have reasonably expected to achieve transfer of a vaccine effective amount of neutralizing antibodies to the fetus based on Faucette to support his contentions. While Dr. Guirakhoo states that Faucette allegedly "acknowledges that inactivated virus vaccines have successfully been used to immunize pregnant women" (EX1002, ¶419 (citing EX1007, 2549)), that disclosure in Faucette says nothing about how to transfer to a fetus a vaccine effective amount of neutralizing antibodies. EX1007, 2549.

152. Dr. Guirakhoo, therefore, fails to establish that a POSA would have had a reasonable expectation of success in arriving at the methods of the Fetal Protection Claims challenged in Grounds VII–XI.

XII. CONCLUSION

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further 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.

Executed on this 18th day of July 2025.

A handwritten signature in black ink, appearing to read 'Dan H. Barouch', with a long horizontal flourish extending to the right.

Dan H. Barouch, M.D., Ph.D.