

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

**PATENT OWNER'S PRELIMINARY RESPONSE
UNDER 37 C.F.R. § 42.107**

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Exhibit No.	Description
2001	Declaration of Dr. Dan H. Barouch in Support of Patent Owner's Discretionary Denial Brief
2002	<i>Curriculum vitae</i> of Dr. Dan H. Barouch
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)
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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/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM142569.pdf (last accessed June 2, 2025)
2017	Schöndorf, I., et al., “Tick-borne encephalitis (TBE) vaccination: Applying the most suitable vaccination schedule,” <i>Vaccine</i> , 25:1470–1475 (2007) (Schöndorf)
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)
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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)
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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

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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)
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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)
2043	Raghupathy, Raj, “Cytokines as Key Players in the Pathophysiology of Preeclampsia,” <i>Medical Principles and Practice</i> , 22(Suppl. 1):8–19 (2013)

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I. INTRODUCTION

Takeda's U.S. Patent No. 11,730,802 ("the '802 patent") is directed to methods of vaccinating against Zika virus ("ZIKV") infection in human subjects or ZIKV disease in a fetus or newborn comprising administering an inactivated ZIKV vaccine to a human subject or a pregnant human subject, respectively. Valneva Austria GmbH's ("Valneva") Petition challenges claims 1–67 of the '802 patent. On June 11, 2025, Takeda statutorily disclaimed claims 1–8, 10, 12–31, 59, and 63 of the '802 patent. EX2005, 3. The Petition's Grounds I and III–VI, challenging claims 1–8, 10, 12–31, 59, and 63, are therefore no longer at issue in this proceeding. Only Grounds II and VII–XI of the Petition addressing claims 9, 11, 32–58, 60–62, and 64–67 ("the Challenged Claims") remain. The Challenged Claims of the '802 patent can be categorized into two groups.

Claims 11, 39, 60–62, and 65–67 (collectively, "the Single Dose/Prime Administration Claims") each recite methods of "vaccinating against Zika virus infection in a human subject" comprising "administering to the human subject a vaccine or immunogenic composition" comprising an antigen from ZIKV "wherein the antigen is an inactivated whole virus ... 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% or more "in a population of at least 20 Zika virus seronegative subjects." In other words, the

Single Dose/Prime Administration Claims require that the inactivated ZIKV vaccine induces the claimed seroconversion rates in a population of human subjects after a single injection of an inactivated ZIKV vaccine, with a “single dose” being the only injection administered to a subject and a “prime administration” being the first injection given before a later-administered booster dose.

Claims 9, 32–58, and 64–67 (collectively, “the Fetal Protection Claims”) each require methods of “vaccinating against Zika virus disease in a fetus or newborn in need thereof” comprising “administering to a pregnant human subject a vaccine or immunogenic composition” comprising an antigen from ZIKV “wherein the antigen is an inactivated whole virus.” The methods further require that “the pregnant human subject adoptively transfers a vaccine effective amount of neutralizing antibodies against Zika virus to the fetus or newborn.”¹

The Petition’s Grounds, however, challenging the Single Dose/Prime Administration Claims and the Fetal Protection Claims are legally and substantively deficient. Valneva, therefore, has failed to establish that it is reasonably likely to prevail with respect to any challenged claim.

¹ Antibodies transferred from mother to fetus during gestation persist in newborns for a period of time after birth. EX2019, 161; EX2026, ¶61.

First, with respect to the Single Dose/Prime Administration Claims, the Petition does not identify where the claimed seroconversion rates in a population of human subjects are present in the prior art. Indeed, the Thomas publication (EX1004) that Valneva advances as the primary reference in each of its Grounds fails to disclose, teach, or suggest the claimed seroconversion rates after a single dose or prime administration in a population of human subjects. Thomas only achieved significant seroconversion in its population of human study subjects after two doses. Other inactivated flavivirus vaccines—the family of viruses to which ZIKV belongs—known in the art before the November 3, 2017 priority date of the ’802 patent likewise failed to achieve the claimed seroconversion rates in populations of human subjects after a single dose or prime administration. Consequently, a POSA would not have reasonably expected that the methods of the Single Dose/Prime Administration Claims could have been achieved before November 3, 2017.

Recognizing that deficiency, Valneva relies on conclusory expert testimony that is based on an incorrect interpretation of the art and is unsupported by any evidence to fill the gap. Indeed, Valneva’s declarant, Dr. Farshad Guirakhoo, alleges that a POSA would have achieved the claimed seroconversion rates by routinely optimizing the dose of Thomas’s inactivated ZIKV vaccine and/or adjuvant type or amount. But Dr. Guirakhoo’s opinions are based on his incorrect

interpretation of Thomas's disclosures and basics of immunology. Dr. Guirakhoo also cites no evidence to support his claim that a vaccine's dose and adjuvant type or amount are result-effective variables that will affect seroconversion rates. In fact, the art demonstrates that adjusting inactivated flavivirus vaccine doses did not result in achieving the claimed seroconversion rates in populations of human subjects after a single dose or prime administration.

Valneva's Petition, therefore, fails to establish that a POSA would have arrived at the methods of the Single Dose/Prime Administration claims with a reasonable expectation of success.

Second, the Petition does not establish why a POSA would have chosen Thomas's inactivated ZIKV vaccine to arrive at the Fetal Protection Claims or would have had a reasonable expectation of success in doing so. Thomas's vaccine failed to achieve significant seroconversion in human subjects after a single dose. Instead, Thomas's vaccine required two doses, given 28 days apart, to induce significant seroconversion in human subjects. But a POSA would have been aware that ZIKV infection during pregnancy can have fatal outcomes (such as congenital defects) in fetuses. A POSA, therefore would have rather sought to use a ZIKV vaccine that induced significant seroconversion quickly, and with as few administrations as possible, in order to attempt to confer protection, whereas Thomas's vaccine required two doses.

Third, Valneva and Dr. Guirakhoo rely 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. The prior art does not support that the proposed combination would have been made, and Valneva and Dr. Guirakhoo fail to establish why a POSA would have sought to use the claimed dose and adjuvant amount to arrive at the claimed methods. It, thus, is apparent that Valneva and Dr. Guirakhoo merely sought out references that disclosed the claimed dose and adjuvant amount.

Lastly, Valneva's Petition fails to demonstrate that a POSA would have had a reasonable expectation of success in arriving at the methods of the Fetal Protection Claims. Valneva seeks to rely on Thomas's experimental adoptive transfer studies involving the transfer of purified vaccine induced antibodies from adult donors to adult animal recipients to allege that a POSA would have had a reasonable expectation of success in arriving at a method of transferring a vaccine effective amount of neutralizing antibodies to a fetus by administering an inactivated ZIKV vaccine to a pregnant human subject. But as Takeda's expert, Dr. Dan Barouch who conceptualized, designed, performed, and reported the data from Thomas's adoptive transfer studies explains, a POSA would have understood that Thomas's adoptive transfer studies are of a fundamentally different process than

the mother-to-fetus transfer of antibodies, and would not have given a POSA a reasonable expectation of success in arriving at the Fetal Protection Claims.

Accordingly, due to the multiple failures in the Petition outlined above, Valneva is not reasonably likely to prevail with respect to any challenged claim. Institution should be denied.

II. THE '802 PATENT AND ITS TECHNICAL BACKGROUND

The '802 patent was filed by Takeda as U.S. Appl. No. 16/761,329, which is the United States national stage entry of International Patent Appl. No. PCT/US2018/059233, filed on November 5, 2018 and claiming its earliest priority to November 3, 2017. EX1001, Cover, (21), (22), (86), (60).

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 member of the *Flaviviridae* family of mosquito-borne viruses, also known as flaviviruses. EX1001, 1:41–45; EX2026, ¶¶3, 38.

Below is a brief technical background on vaccines and ZIKV that a POSA would have understood before November 3, 2017, and a discussion of the challenged claims to aid in understanding the deficiencies in Valneva’s Petition that warrant denying institution.

A. Brief Technical Background On Vaccines

The goal of a POSA when vaccinating a subject is to stimulate the subject's immune system to generate antibodies that neutralize a target infectious agent, such as viruses. EX2008, 709; EX2026, ¶¶42–44. Such antibodies are known in the art as “neutralizing antibodies,” and they serve to prevent or treat infection or limit the consequences of infection. EX2008, 709; EX2026, ¶42.

Those in the field of vaccinology measured the amount, i.e., “titer,” of neutralizing antibodies that subjects generate after being administered a given vaccine. EX2009, 126; EX2026, ¶42. If the investigator detected neutralizing antibodies above a certain pre-determined value that indicated a significant immune response in the vaccinated subject, the subject would be 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 neutralizing titers of $\geq 1:20$ as indicative of seroconversion); EX2026, ¶43. By assessing multiple subjects of a vaccinated population, investigators can determine the seroconversion rate after vaccination. EX2026, ¶¶42–44.

1. Live-attenuated and inactivated virus vaccines were known to typically induce differing levels of immune responses.

Before November 3, 2017, the art disclosed that different types of vaccines, such as live-attenuated vaccines and inactivated virus vaccines, were known to typically elicit different levels of immune response after an initial dosing. EX2012; EX1004; EX2013, 171. EX2026, ¶¶44-49.

Live-attenuated vaccines use a weakened, i.e., “attenuated,” version of the virus that can still replicate in the vaccinated subject (albeit to lower levels than the non-attenuated counterpart). EX2014, 156, 164; EX2026, ¶46. Live-attenuated vaccines were known by those in the field to be able to typically stimulate a significant immune response after one dose. EX2014, 164; EX2013, 171; EX2026, ¶46. A POSA would have understood that this was the result of at least two factors. EX2026, ¶¶46–47. First, the amount of antigen available for presentation to the recipient’s immune system is amplified due to the virus’s continued replication in the subject administered the vaccine. EX2014, 164; EX2013, 171; EX2026, ¶46. Second, live-attenuated viruses are not subjected to a treatment process that would inactivate the virus, and therefore, the virus’s proteins that act as antigens remain intact. EX2014, 164.

Unlike *live-attenuated* vaccines, prior-art *inactivated* virus vaccines were typically unable to provide a significant immunogenic response after a single dose. EX2026, ¶¶48–49. This is because, one, the inactivated virus in such vaccines

cannot replicate because the inactivation process “destroy[s] infectivity while retaining immunogenicity.” EX2014, 156, 158; EX2026, ¶49. And, two, the art disclosed that a downside of the inactivation process was that the “treatment used to eliminate infectivity of inactivated virus vaccines may be damaging enough to modify immunogenicity.” EX2014, 158; EX2026, ¶49. In other words, the inactivation processes damaged the virus’s proteins that act as antigens, impairing their ability to trigger a sufficient immune response with a single vaccine dose. The art reported that those two aspects of inactivated virus vaccines typically resulted in “an immune response shorter in duration, narrower in spectrum for viral antigens, weaker cell-mediated and mucosal immune responses,² and possibly less effective in preventing viral entry [into cells].” EX2014, 158; EX2026, ¶49. It was, therefore, known in the art that effective vaccination treatment with inactivated virus vaccines minimally “comprise[d] two or three injections,” with “further ‘booster’ doses [likely] be[ing] required at intervals to maintain protective immunity.” EX2014, 158; EX2026, ¶¶45–49.

² 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; EX2026, ¶49 n.1.

2. A subject's immune system mounts a primary response to the first dose of a vaccine that is in general lower than the immune system's heightened response to a second dose.

Exposure of a subject to an antigen for the first time results in the body mounting a primary immune response. EX2035, 13420; EX2036, 429; EX2026, ¶50. During that primary immune response, the subject's immune system recognizes the antigen as “new” and begins the process of producing neutralizing antibodies against the antigen. EX2035, 13420; EX2037, 452–453; EX2036, 429; EX2026, ¶50. The immune system also generates memory B and T cells during the primary immune response, which remain in the body for an extended period of time, sometimes a lifetime, after the first exposure to the antigen. EX2035, 13420; EX2037, 452–453, 455; EX2026, ¶¶50–51. The primary immune response can often take several weeks to develop. EX2035, 13420; EX2037, 452–453, 455; EX2026, ¶50.

When the subject is then exposed to the antigen for a second time, the immune system then generally mounts a more rapid and effective response, known as the “anamnestic response.” EX2037, 451; EX2036, 448–449, 451–455; EX2026, ¶51. The anamnestic response is a heightened response mediated by the memory B and T cells that were generated by the body's immune system during the primary immune response. EX2037, 451; EX2036, 448–449, 451–455; EX2026, ¶¶50–51. During the anamnestic response, when the memory B or T cells

generated during the primary immune response encounter the antigen again, the memory B or T cells become rapidly activated. EX2037, 451; EX2036, 448–449, 451–455; EX2026, ¶¶50–51. That rapid activation then in general leads to a greater immune response, including, in general, the production of significantly greater amounts of neutralizing antibodies compared to those generated during the primary immune response. EX2035, 13423; EX2037, 451–452; EX2036, 450–452; EX2026, ¶51. The anamnestic response aims to provide the body with both rapid and long-term immunity against a given antigen after the body’s first exposure to the antigen. EX2035, 13423; EX2037, 451–452; EX2036, 450–452; EX2026, ¶¶51–52.

The anamnestic response is also the general basis behind booster doses that are given at least several weeks or months apart with vaccines. EX2037, 455; EX2026, ¶¶51–52. When a subject is administered a vaccine for the first time, the subject’s immune system will mount a primary immune response that can take several weeks to generate an initial amount of neutralizing antibodies. EX2035, 13420; EX2037, 452–453, 455; EX2026, ¶¶51–52. Upon administering the second dose several weeks or months later, the immune system is primed. EX2037, 451; EX2036, 448–449, 451–455; EX2026, ¶¶50–52. The anamnestic secondary immune responses then kick in and generally lead to the rapid generation of greater

titers of neutralizing antibodies typically with a greater affinity to the vaccine's antigen, providing improved immunity. EX2036, 450–452; EX2026, ¶¶50–52.

B. Before November 3, 2017, Inactivated Flavivirus Vaccines In The Art Required Multi-Dose Schedules To Effect Sufficient Seroconversion In A Population of Human Subjects.

As mentioned, ZIKV is a member of the flavivirus family of mosquito-borne viruses. Other members of this family are Japanese encephalitis virus (“JEV”), yellow fever virus (“YFV”), Dengue virus (“DENV”), and tick-borne encephalitis virus (“TBEV”). EX1001, 1:41–45; EX2026, ¶¶3, 38, 53.

Before November 3, 2017, various inactivated virus vaccines for JEV, YFV, DENV, and TBEV had been reported in the art. EX2026, ¶¶53–54. Studies showed that single-dose administrations of those vaccines failed to achieve an at least 60% seroconversion rate in a population of human subjects as determined using a neutralizing antibody titer of at least 1:10, as had been used in the art for flavivirus vaccines, shown in the table below. *Id.*

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 ³	100% – measured 10 days after 2 nd administration

³ Monath used a cut-off titer of $\geq 1:10$ for indicating seropositivity. EX2015, Table 2; EX2026, ¶54 n.2. At that cut-off, Monath only observed 46% of the human subject population achieving a titer of $\geq 1:10$ after a single administration. EX2015, Table 2; EX2026, ¶54 n.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	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
DENV-1 PIV (EX2010, Table 3)	DENV	5 µg Titer ≥ 1:10	First Dose – Day 0 Second Dose – Day 28	10% (5 µg) ⁴ – measured 28 days after 1 st administration	100% – measured 14 days after 2 nd administration
Encepur (Conv. Schedule; Group C)	TBEV	1.5 µg Titer ≥ 1:10	First Dose – Day 0 Second Dose – Day 28	29% – measured 21 days after 1 st administration	95% – measured 14 days after 2 nd administration

⁴ 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; EX2026, ¶54 n.3.

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

⁵ Schöndorf (EX2017) also evaluated other 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). EX2017, 1472; EX2026, ¶54 n.4. At Study Day 21, on which the seroconversion

EX2026, ¶54.

As shown above, inactivated flavivirus vaccines investigated in human subjects before November 3, 2017 required more than one dose to achieve a seroconversion rate of at least 60% in the vaccinated human population. EX2026, ¶¶53–55. Given that, a POSA would not have reasonably expected to arrive at an inactivated ZIKV vaccine that could achieve the claimed seroconversion rates in a population of human subjects after a single dose. *Id.*

C. Before November 3, 2017, ZIKV Emerged As A Threat, Particularly To Travelers And Pregnant Women.

Before November 3, 2017, the earliest effective filing date of the '802 patent, ZIKV had spread in a “hemispheric-wide epidemic” throughout the Americas, including the U.S., since it was introduced into Brazil in 2013. EX1001, 1:41–48; EX2026, ¶56. The spread of ZIKV became concerning because ZIKV infection in pregnant women became known to give rise to microcephaly and “catastrophic neurodevelopmental outcomes in human fetuses,” which evidence

rate (cut-off 1:10) was determined for the first time, subjects in Groups R and A had already received the second dose. Even after receiving a second dose, the seroconversion rates remained below 60% (i.e., 56% and 53%, respectively).

EX2017, 1472, FIG. 2; EX2026, ¶54 n.4.

suggested was a result of ZIKV destroying neurological stem cells in the fetus.

EX2031, 1084; EX2003, 474; *see also* EX2020, 1981–1983, 1985; EX2026, ¶57.

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; EX2026, ¶57. ZIKV infections that occur later in pregnancy also had been associated with dramatic outcomes. EX2020, 1982; EX2026, ¶57. While vaccinating against ZIKV at any pregnancy stage, therefore, would have been important, a ZIKV infection’s possible detrimental effects would have made the speed of onset of the subject’s immune response induced by a ZIKV vaccine an important element of a ZIKV vaccine so as to produce a sufficient titer of neutralizing antibodies after as few administrations as possible — rather than waiting multiple weeks to provide booster doses — given that “the most severe manifestations are associated with infections in the first and second trimesters.” EX2031, 1081; EX2026, ¶¶56–62.

Yet, before November 3, 2017, inactivated flavivirus vaccines failed to show significant rates of seroconversion in populations of human subjects after a single dose. *See* §II.B., *supra*. In fact, for ZIKV vaccines, the Thomas reference relied upon heavily by Valneva had a negligible seroconversion rate in a population of human subjects after a single dose and nowhere to the extent required by Takeda’s claimed methods, as explained in detail below. EX1004, 42:4–20; EX2026, ¶¶60,

72–80; *see also* §III.A.1.a., *infra*. Consequently, a POSA would have expected that an inactivated ZIKV vaccine would have also required multiple doses, administered several weeks apart, to induce sufficient seroconversion in a population of human subjects, as discussed below in §III.A. EX2026, ¶¶60, 72–80, 109–112.

In contrast, a POSA would not have expected to achieve a method of vaccinating against ZIKV with an inactivated ZIKV vaccine to provide for the claimed seroconversion rates after a single dose in a population of human subjects—thus providing for rapid seroconversion. EX2026, ¶¶60, 72–80, 109–112; *see also* §III.A., *infra*. The claimed invention of the Challenged Claims achieved such a method, providing for methods of seroconverting at least 60% of a population of human subjects after a single dose or prime administration and for transferring a vaccine effective amount of neutralizing antibodies from a pregnant human subject to the fetus or newborn. EX2026, ¶¶61.

The present invention of the Challenged Claims, therefore, addresses the risks of ZIKV transmission, e.g., for pregnant individuals or individuals that may become pregnant, travelers, and deployed members of the military who seek a sufficient immune response quickly and with as few administrations as possible. EX1001, 8:2–7; EX2026, ¶¶56–62. The claimed invention also provides a benefit when there may be an unexpected outbreak of ZIKV. Indeed, as the '802 patent

recognizes, “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; EX2026, ¶61.

D. The Challenged Claims

The Fetal Protection Claims: Independent claims 9, 41, 43, 49, 53, 54, 57, and 58, and their dependent claims 32–40, 42, 44–48, 50–52, 55, 56, and 64–67 each require methods of “vaccinating against Zika virus disease in a fetus or newborn in need thereof” comprising “administering to a pregnant human subject a vaccine or immunogenic composition” comprising an antigen from ZIKV “wherein the antigen is an inactivated whole virus.” EX1001, 123:24–39, 125:1–128:26; EX2026, ¶39. The methods further require that “the pregnant human subject adoptively transfers a vaccine effective amount of neutralizing antibodies against Zika virus to the fetus or newborn.” EX1001, 123:24–39, 125:1–128:26; EX2026, ¶39.

Given that those claims are directed to fetal protection against ZIKV, as discussed above in §II.C., a ZIKV infection’s possible detrimental effects in pregnant individuals would have made the speed of onset of the subject’s immune response, after as few administrations as possible, an important consideration. EX2026, ¶¶56–62, 67.

The Single Dose/Prime Administration Claims: Independent claim 11, and its dependent claims 60–62, and claims 39, and its dependent claims 65–67 (collectively, “the Single Dose/Prime Administration Claims”), recite achieving seroconversion rates of at least 60% (claims 11 and 39), at least 80%, 90%, or 95% (claims 60–62), or at least 70%, 80%, or 90% (claims 65–67) in human subjects after a single dose or prime administration of an inactivated ZIKV vaccine or immunogenic composition. EX1001, 123:40–52, 125:25–29, 127:24–128:26; EX2026, ¶40. In other words, those claims require inducing the claimed seroconversion rates after a single injection of an inactivated ZIKV vaccine, with a “single dose” being the only injection administered to a subject and a “prime administration” being the first injection given before a later-administered booster dose. EX2026, ¶40.

As discussed above in §II.B., inactivated flavivirus vaccines known in the art before November 3, 2017, were unable to achieve a seroconversion rate of at least 60% in a population of human subjects after a single dose. EX2026, ¶¶53–54.

E. Prosecution History Of The '802 Patent

During prosecution of the application that issued as the '802 patent, the Examiner rejected then-pending claims 65–74, 78–90, 92–96, 103–106, 121, and 122 as allegedly anticipated and/or obvious over Barbero (EX1005). EX1003, 87–90. And the Examiner objected to then-pending claims 75–77, 97–102,

107–119, 123, and 124 for being dependent upon a rejected base claim, but allowable if rewritten in independent form. *Id.*, 87.

Takeda responded by amending pending independent claim 65 to incorporate subject matter of its dependent claims 70 and 75. *Id.*, 53–54, 147. And Takeda amended pending claim 91 to be an independent claim. *Id.*, 57. Pending claim 65, and its dependent claims 66–73, 75, 77–90, 92–96 and 125, and pending claim 91, and its dependent claim 129, issued as '802 patent claims 1–8, 10, 12–31, 59, and 63 that are no longer at issue in this proceeding. *Compare* EX1003, 53–57, 62 *with* EX1001, 121:60–67, 122:60–123:23, 123:35–39, 123:53–124:61, 127:20–23, 128:10.

With respect to the Challenged Claims, Takeda amended pending independent claim 74 to incorporate the subject matter of claim 100. *Id.*, 54, 58, 151. And pending claims 76, 107, 109, 115, 119, 120, 123, and 124 were written into independent form. *Id.*, 55, 59–62. Pending claim 74, and its dependent claims 97–106, 110–114, 121, 122 and 131–133, and pending claims 76 (and its dependent claims 126–128), 107 (and its dependent claim 108), 109, 115 (and its dependent claims 116–118), 119, 120 (and its dependent claim 130), 123, and 124, issued in order as '802 patent claims 9, 11, 32–58, 60–62, and 64–67, as shown in the table below. *Compare* EX1003, 54, 55, 58–63 *with* EX1001, 123:24–52, 124:62–127:19, 127:24–128:26.

Pending Claim	Issued Claim	Rejected or Indicated as Allowable by the Examiner
74, 103–106, 121, and 122	9, 37–40, 55, and 56	Rejected over Barbero
97–102 and 110–114	32–36 and 44–48	Indicated as allowable
131–133	64–66	Added after Non-Final Office Action
76	11	Indicated as allowable
126–128	60–62	Added after Non-Final Office Action
107 and 108	41 and 42	Indicated as allowable
109	43	Indicated as allowable
115–118	49–52	Indicated as allowable
119	53	Indicated as allowable
120	54	Rejected for allegedly being indefinite
130	64	Added after Non-Final Office Action
123	57	Indicated as allowable
124	58	Indicated as allowable

Valneva alleges that the Examiner should not have allowed the Challenged Claims in view of the art it advances in the Petition. Pet., 15–17. But as discussed below in §III, the art Valneva advances fails to render the Challenged Claims

unpatentable. Indeed, the Thomas publication (EX1004), which Valneva uses as the primary reference in each of Grounds II and VII-XI still at issue, fails to disclose, teach, or suggest the claimed seroconversion rates of the Single Dose/Prime Administration Claims, even in combination with other relied-upon art. EX2026, ¶¶70–107. Nor would a POSA have arrived at the claimed seroconversion rates in humans with a reasonable expectation of success in view of Thomas and what was known in the art about inactivated flavivirus vaccines, which required at least two doses to achieve at least 60% seroconversion in a population of human subjects. *See* §III.A.1., *infra*; EX2026, ¶¶91–117. A POSA, furthermore, would not have been motivated to arrive at the Fetal Protection Claims with a reasonable expectation of success using Thomas’s inactivated ZIKV vaccine, given that Thomas’s vaccine required two doses to achieve seroconversion in human subjects. *See* §III.B., *infra*; EX2026, ¶¶118–152.

III. EACH OF THE PETITION’S GROUNDS II AND VII–XI FAILS TO ESTABLISH A REASONABLE LIKELIHOOD OF PREVAILING.

Grounds II and VII–XI fail to establish that Valneva has a reasonable likelihood of prevailing with respect to any challenged claim. As the “master of its own petition,” Valneva cannot now go back and attempt to fill the holes in its Petition and its expert’s testimony. *Qualcomm v. Apple*, 134 F.4th 1355, 1367 (Fed. Cir. 2025). Denying institution is therefore warranted.

A. Valneva’s Challenge In Grounds II And VII Fails To Establish Unpatentability Of The Single Dose/Prime Administration Claims.

In Grounds II and VII challenging the Single Dose/Prime Administration Claims, Valneva exclusively relies on conclusory and unsupported testimony from its declarant, Dr. Guirakhoo, to fill in gaps in the prior art. *See* §§III.A.1.–III.A.2.; EX2026, ¶¶70–107. Valneva and Dr. Guirakhoo also fail to establish that a POSA would have had a reasonable expectation of success in arriving at the Single Dose/Prime Administration Claims. *See* §§III.A.2–III.A.3.; EX2026, ¶¶91–117.

1. Valneva’s Petition relies exclusively on conclusory expert testimony to fill gaps in the prior art.

The Single Dose/Prime Administration claims require achieving various rates of seroconversion of at least 60% or greater in a population of human subjects 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, 127:24–128:26; EX2026, ¶¶40, 70. The Petition recognizes that Thomas, the primary reference relied upon, “does not teach this rate after a single dose.” Pet., 26; EX1002, ¶173. To fill this gap in the art, Valneva relies exclusively on the testimony of Dr. Guirakhoo who alleges that Thomas’s vaccine could be routinely optimized to achieve the claimed seroconversion rates in a population of human subjects. Pet., 28, 30; EX1002, ¶¶178, 185, 192, 199. But, Dr. Guirakhoo fails to cite any evidence to support his allegations. EX1002, ¶¶178, 185, 192, 199;

EX2026, ¶¶70–107; *see also* §III.A., *infra*. Dr. Guirakhoo also incorrectly interprets the prior art and fails to take into account what was known about inactivated flavivirus vaccines before November 3, 2017. EX2026, ¶¶81–90, 109–112; *see also* §§III.A.1.b. and III.A.3.a., *infra*. Thus, Dr. Guirakhoo does not establish that the dose or adjuvant in a vaccine are result-effective variables. EX2026, ¶¶104–107; *see also* §III.A.2., *infra*.

Accordingly, Grounds II and VII fail to establish unpatentability of the Single Dose/Prime Administration Claims. ¶¶70–117.

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

Dr. Guirakhoo does not identify where 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 can be found in the prior art. EX1002, ¶¶162–201; EX1001, 123:40–52, 125:25–29, 127:24–128:26; EX2026, ¶¶71–74. Indeed, Dr. Guirakhoo ***cannot*** demonstrate where the claimed seroconversion rates in a population of human subjects are found in the asserted art because Thomas ***does not disclose*** that its inactivated ZIKV vaccine induced the claimed seroconversion rates in a population of human subjects after a single dose or prime administration. EX1004, 42:4–20; EX2026, ¶¶75–80, 91–99.

More specifically, Thomas administered its ZIKV vaccine to human subjects at Day 0 and Day 28. EX1004, 42:4–20; EX2026, ¶75. Using a neutralizing antibody titer of 1:10 to evidence seroconversion, Thomas reported geometric mean titers (GMTs)⁶ in a table in Thomas’s Example 5. EX1004, 42:4–20; EX2026, ¶76. In Thomas’s table, Day 0 corresponds to “Day 1” and Day 28 corresponds to “Day 29”. EX1004, 42:4–20; EX2026, ¶¶75–76. Thomas’s table is reproduced below with a box outlining the neutralizing 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*). EX2026, ¶76.

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 in a neutralization assay. EX2023, 141; EX2026, ¶94.

Time Point ^a	Statistic	5 mcg ZPIV				Placebo
		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); EX2026, ¶76.

As shown in the Thomas’s table reproduced above, Thomas observed that *none* of the populations of subjects in the three groups (16-0033, 16-0062, and Z0001) that received Thomas’s inactivated ZIKV vaccine achieved mean titers (“GMT”; arrows) greater than 1:10 after a single dose or prime administration.⁷ EX1004, 42:4–20; EX2026, ¶¶77–78. In other words, Thomas’s vaccine *did not result in mean titers above Thomas’s seroconversion cut-off* in any of the three populations of human subjects in Thomas’s study. EX2026, ¶¶77, 79.

Thomas measured the GMTs across the three groups (“All”) to be 1:5.8 on 14 days (Day 15; Group 1 = 1:5.0, Group 3 = 1:8.6) and 1:7 on 28 days (Day 29;

⁷ Thomas reports the GMT using the integer value of the right hand side of the neutralizing antibody titer ratio, e.g. a GMT of 5.8 is a ratio of 1:5.8. EX2026, ¶78.

Group 1 = 1:5.5, Group 2 = 1:8.5, Group 3 = 1:8.7) after the prime administration and before the second (boost) administration. EX1004, 42:4–20; EX2026, ¶78. Indeed, both values of GMTs of 1:5.8 and 1:7, as well as the GMTs for each Group individually, are below the 1:10 titer cutoff Thomas used to evidence seroconversion, as even Thomas acknowledged: “after the first dose of vaccine [] mean titers remain[ed] below the 1:10 titer cutoff.” EX1004, 42:9–10; EX2026, ¶78. Consequently, Thomas’s inactivated ZIKV vaccine *did not induce* a seroconversion rate of at least 60% in a population of 20 ZIKV seronegative human subjects after a single dose or prime administration. EX1004, 42:4–20; EX2026, ¶¶75–79.

In fact, Thomas had to use a second (boost) dose to seroconvert greater than 60% of the population of human subjects who received Thomas’s inactivated ZIKV vaccine. EX1004, 42:4–20; EX2026, ¶79. That is not what the Single Dose/Prime Administration Claims require. The claims require inducing the claimed seroconversion rates in a population of human subjects after a single dose or prime administration. EX2026, ¶¶40, 70. Thomas only observed GMTs greater than 1:10 (Thomas’s seroconversion cutoff) at Day 43. EX1004, 42:4–20; EX2026, ¶79. That is 14 days after Thomas gave the *second* (boost) administration of its inactivated ZIKV vaccine. EX1004, 42:4–20; EX2026, ¶79.

Thomas thus fails to disclose the claimed seroconversion rates in a population of human subjects after a single dose or prime administration and Valneva and Dr. Guirakhoo do not point to where it is otherwise found in the prior art as required by 37 C.F.R. § 42.104(b)(4). EX2026, ¶¶72–80.

b. Dr. Guirakhoo incorrectly relies on Thomas’s seroprotection data from mice that a POSA would have known are often not predictive of responses in human subjects.

Rather than address Thomas’s actual data in human subjects head on, Dr. Guirakhoo seeks 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.” EX1002, ¶176 (citing EX1004, 4:15–22); EX2026, ¶81. *But Thomas’s own data contradict Dr. Guirakhoo’s assertion with respect to a population of human subjects.* EX2026, ¶¶81–90.

Thomas only observed significant seroconversion in a population of human subjects after the subjects received *two* doses of Thomas’s vaccine, which were administered 28 days apart. EX1004, 42:4–20. EX2026, ¶¶72–79. Thomas, moreover, only observed that a single dose induces protection when its vaccine was administered to *mice, not humans*. EX2026, ¶82. But the challenged Single Dose/Prime Administration Claims require inducing the claimed seroconversion rates in a population of *human* subjects, not mice. *Id.* Thomas *failed to achieve* mean antibody titers in a population of human subjects above the seroconversion

cut-off value of 1:10 after a single dose or prime administration. EX1004, 42:4–20; EX2026, ¶¶76-79, 82.

It was also well-known in the art that pre-clinical studies in mice used to investigate immunological responses *are often not predictive* of such results in humans. EX2021, 835–836; EX2018, 5; EX2026, ¶83. The art reported that “mice are lousy models” and the inbred laboratory mouse strains that are used “skew the regulation of the immune response.” EX2021, 835–836; EX2026, ¶83. The art also provided 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; EX2026, ¶83. Laboratory mice, moreover, 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,” making them substantially different from humans that are genetically diverse, exposed to pathogens throughout life, and long-lived, resulting in humans evolving to be more invested in individual survival, and the art notes that could create differences in immunological responses between mice and humans. EX2021, 836; EX2027, 183–185; 2030, 516; EX2029, 36; EX2026, ¶83.

Vaccine experts, including Dr. David Weiner and Dr. Paul Offit, moreover, have stated that “[m]ice lie and monkeys exaggerate” in terms of vaccine immune responses. EX2025, 224; EX2024, 719; EX2026, ¶84. And, as Dr. Barouch states, many of those in the field of vaccinology have shared this perspective before November 3, 2017. EX2026, ¶84.

Dr. Guirakhoo’s reliance on Thomas’s statement about “100% complete protection” after a single dose as being applicable to the Single Dose/Prime Administration Claims, therefore, is factually incorrect. EX2026, ¶¶85–90. Thomas only observed such a result in mice—not in humans, the subject population required by the claims. EX1004, 12:14–33, FIG. 7a, 42:4–20; EX2026, ¶¶82, 85.

In fact, the mice studies Thomas performed exemplify the concerns the art had about mice often not being predictive of human immunological responses. Thomas injected Balb/c mice with a single 1 µg dose of Thomas’s inactivated ZIKV vaccine. EX1004, 32:20–26; EX2026, ¶86. Balb/c mice, however, are highly inbred mice that are genetically identical to each other. EX2021, 835–836; EX2026, ¶86. Yet, such inbreeding “creates a wealth of homozygous recessive defects that skew the regulation of the immune response.” EX2021, 835–836; EX2026, ¶86.

Thomas's mice were also lab-dwelling cage animals that typically would not have been exposed to any pathogens before being injected with Thomas's inactivated ZIKV vaccine, "this raises the concern that the immune system of [such] mice is less representative of that of adult humans." EX2027, 181; EX2026, ¶87. Thus, once injected, they are exposed to a foreign antigen (here, ZIKV) for the first time ever in their lives, resulting in an immune response that is not correlative to that of an adult human that has been exposed to multiple, if not countless, pathogens throughout their life. EX2027, 183–185; 2030, 516; EX2026, ¶87. A POSA would have also known that such pathogen-naïve mice can have exaggerated immune responses to antigens. EX2029, 366; EX2026, ¶87.

The 1 µg dose Thomas used is also very high in comparison with the human dose on a per weight basis, given the average weight of a Balb/c mouse. EX2026, ¶88. The average adult Balb/c mouse weighs 25 g. EX2039; EX2026, ¶88. Thomas, therefore, used a dose of about 40 µg/kg. EX2026, ¶88. In comparison, the average human weighs about 70–80 kg, and the 5 µg dose Thomas administered to its human subjects, therefore, was about 0.0625–0.071 µg/kg. EX2034, Table 3; EX2026, ¶88. Thomas thus administered about 560-fold to about 640-fold higher of a dose on a per weight basis to its mice. EX2026, ¶88. Thomas would have had to administer a 2,800–3,200 µg dose to his human subjects for the dose to be equivalent to what Thomas administered to mice. *Id.* Such a dose is *far*

from anything feasible because of practical limits on dosing or manufacturing, such as costs of goods. *See, e.g.*, EX1004 42:4–20; EX2010, Table 3; EX2015, Table 2; EX2016, 20; EX2017, 1471–1472; EX2026, ¶88. Indeed, the maximum single dose Thomas tested in humans was 5 µg, which is line with doses for other inactivated flavivirus vaccines. *Id.*

A POSA, therefore, would not have expected Thomas’s seroprotection data from mice to be able to be extrapolated to what would have occurred in humans. EX2026, ¶¶81–90. Indeed, as set forth above, Thomas provides its own internal evidence regarding how Thomas’s vaccine behaved in human subjects that contradicts Dr. Guirakhoo’s position. *Id.* The same vaccine Thomas administered to mice did not result in significant seroconversion in a population of human subjects after a single dose, but rather two doses, as would have been expected by a POSA in view of the typical characteristics of inactivated vaccines and because responses in mice are often not predictive of responses in humans. *Id.* And Thomas would not have been able to get anywhere near the dose per weight that Thomas administered to mice in human subjects. *Id.*

2. **Dr. Guirakhoo provides no evidentiary support for his claim that a POSA would have had a reasonable expectation of success in achieving the claimed seroconversion rates after a single dose or prime administration in a population of human subjects.**

Acknowledging that Thomas does not disclose the claimed seroconversion rate in a population of human subjects after a single dose or prime administration, Dr. Guirakhoo, relies on four inaccurate and unsupported statements to come to the conclusion that a POSA could have routinely optimized the ZIKV antigen dose and/or adjuvant amount or type to achieve the claimed seroconversion rate in a population of human subjects after a single dose or prime administration EX1002, ¶¶178, 471, 517; EX2026, ¶¶91–107. This provides additional evidence of that Valneva has not established a reasonable likelihood of prevailing with respect to any challenged claim.

- a. **Dr. Guirakhoo incorrectly alleges that a single 10 µg dose of Thomas’s vaccine would have given an immune response equivalent to that of two 5 µg doses given weeks apart.**

First, in alleging that a POSA would routinely optimize the dosage for Thomas’s vaccine and arrive at using 10 µg,⁸ Dr. Guirakhoo incorrectly alleges

⁸ Although Dr. Guirakhoo makes this allegation in the context of other claims that recite administering a 10 µg dose of Thomas’s vaccine, it is relevant to show the overall fallacy of his routine optimization allegations. EX2026, ¶92.

that a single 10 µg dose of Thomas's vaccine would be equivalent to the two 5 µg doses Thomas gave weeks apart in a prime-boost dosing regimen. EX1002, ¶¶369, 382, 516; EX2026, ¶92. Dr. Guirakhoo is incorrect. EX2026, ¶¶92–98.

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

EX1002, ¶¶369, 382, 516 (internal citations omitted).⁹

Dr. Guirakhoo's statement is remarkable given (1) Thomas's study data from human subjects; and (2) it is contrary to what was well-known in the art about fully established principles of immune responses. EX2026, ¶¶92–107.

⁹ Emphases are added throughout, unless otherwise noted.

First, as discussed above in §III.A.1.a., Thomas’s inactivated ZIKV vaccine only induce negligible seroconversion in the human study population when administered as a first 5 µg dose. Yet, Dr. Guirakhoo states that a POSA would have reasonably expected that a single 10 µg dose “would provide *a similar ... immunological response and protection* against Zika virus *compared to a single 5 µg dose.*” EX1002, ¶¶369, 382, 516; EX2026, ¶94. Achieving a similar immunological response as a single 5 µg dose of Thomas’s vaccine with a 10 µg dose, however, would not have led to the claimed seroconversion rates in a population of human subjects. EX2026, ¶94. Thomas did not achieve the claimed rates with a single 5 µg dose. 1004, 42:4–20; EX2026, ¶94.

Second, as discussed above in §II.A.2., when a subject’s immune system is exposed to a foreign antigen for the first time, the subject’s immune system mounts a primary immune response that takes several weeks to develop. EX2035, 13423; EX2037, 451-452; EX2036, 448–449, 451–455; EX2026, ¶¶50–52, 95. Upon a second exposure, the subject’s anamnestic response¹⁰ generally results in a more

¹⁰ As discussed above in §II.A.2., the body’s anamnestic response is the result of the immune system encountering a given antigen again after a first exposure and usually rapidly generating a greater amount of neutralizing antibodies against the antigen compared to the body’s first encounter with the antigen. EX2026, ¶¶50–52.

rapid response and a significantly greater amount of neutralizing antibodies compared to the primary response. EX2035, 13423; EX2037, 451-452; EX2036, 448-449, 451-455; EX2026, ¶¶50-52, 95.

Accordingly, when Thomas administered the first 5 µg dose of its vaccine to its ZIKV seronegative human subjects, they would have mounted a primary immune response. EX2026, ¶96. And when Thomas administered its first dose, Thomas did not observe seroconversion at the claimed rates in the human study population. EX1004, 42:4-20; EX2026, ¶¶76, 96. Only upon administering a second 5 µg boost dose, 28 days later, did Thomas observed seroconversion in greater than 88% of the study population. A POSA would have understood that the significant uptick in seroconversion rate after the second dose of Thomas's vaccine was because of the study subjects' anamnestic response. EX1004, 42:4-20; EX2037, 451; EX2035, 13420; EX2036, 448-449, 451-455; EX2026, ¶96. The immune response Thomas observed after two 5 µg doses, therefore, does not correlate to the response that would have been seen from a first, single 10 µg dose of the vaccine. EX2026, ¶96. The initial exposure to ZIKV in subjects after receiving a first, single 10 µg dose would have only resulted in an insufficient primary immune response. EX2035, 13420; EX2036, 429; EX2037, 452-453; EX2026, ¶¶50-52, 95-98. And a POSA would have understood that the primary immune response from a first, single 10 µg dose with Thomas's inactivated ZIKV

vaccine would not have been as heightened as the anamnestic response Thomas observed after giving a second 5 µg dose of Thomas's inactivated ZIKV vaccine. EX2037, 451; EX2035, 13420; EX2036, 448–449, 451–455; EX2026, ¶¶50–52, 95–98.

Consequently, Dr. Guirakhoo's testimony is contradicted by the fully established principles of immunology set forth above. EX2026, ¶¶92–98. And a POSA understanding that would not have sought to equate the primary and anamnestic immune response of two 5 µg doses of Thomas's inactivated ZIKV vaccine given weeks apart to a primary immune response of a single 10 µg dose of Thomas's inactivated ZIKV. *Id.*

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

Second, Dr. Guirakhoo incorrectly applies Thomas's data from inbred laboratory 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 would have been effective and safe. EX1002 ¶178; EX1004 4:15–22, 18:17–20; EX2026, ¶¶99–101. But, responses in inbred laboratory mice are often not predictive of responses in humans because inbred laboratory mice can overestimate human immune responses. EX2021, 835–836; EX2018, 5; EX2026, ¶¶81–87, 99; *see also* §III.A.1.b. And as discussed

in §II.D., the Single Dose/Prime Administration Claims require achieving the claimed seroconversion rates after a single dose in a population of *human subjects*. EX1001, 123:40–52.

On a per weight basis, the dose Thomas administered to its inbred mice was nowhere near the dose Thomas administered (or could have administered) to human subjects. *See* §III.A.1.b.; EX2026, ¶¶88, 100. Thus, the immune response induced in Thomas’s pathogen-naïve, inbred mice would not have been expected to correlate to an adult human response, where the adult humans have previously been exposed to numerous pathogens and administered a 600-fold lower dose per weight. EX2027, 183–185; EX2029, 366; EX2030, 516; EX2026, ¶100. Indeed, Thomas did not achieve the claimed seroconversion rates after a single dose in its human study subjects. EX1004, 42:4–20; EX2026, ¶¶72–80.

Dr. Guirakhoo, therefore, incorrectly applies Thomas’s statement based on data from mice to what he alleges would have happened in humans. EX2026, ¶¶99–101. His opinions in this regard should be given little weight.

c. Thomas’s disclosure regarding exploring a range of antigen doses does not support Dr. Guirakhoo’s conclusory allegations.

Third, Dr. Guirakhoo’s reliance on Thomas’s statement that “ZIPV [sic] is explored across a range of antigen doses” is misplaced and does not support that a POSA could have reasonably expected to achieve the claimed seroconversion rates

with Thomas's inactivated ZIKV vaccine in a population of human subjects after a single dose or prime administration. EX1002, ¶124; EX2026, ¶¶102–103.

In fact, as discussed above in §II.B., before November 3, 2017, inactivated flavivirus vaccines known in the art did not provide greater than a 60% seroconversion rate in a population of human subjects after a single dose. EX2016, 20; EX2015, Table 2; EX2010, Table 3; EX2017, 1471–1472; EX2026, ¶¶53–55, 102. And Dr. Guirakhoo's attempt to rely on Thomas's 92% seroconversion rate in humans after two doses is misplaced, as Thomas failed to achieve the claimed seroconversion rates in the population of human subject it studied after a single dose. EX1002, ¶¶194–200; EX1004, 42:4–20; EX2026, ¶102. Moreover, as discussed, Dr. Guirakhoo wrongly equates two 5 µg doses with a single 10 µg dose to argue that adjusting the dose of Thomas's vaccine would result in greater seroconversion at higher doses. EX2026, ¶¶92–98, 102. The increased immune response upon receiving a second 5 µg dose, i.e., the anamnestic response, that resulted in seroconversion in greater than 88% of the population of Thomas's human study subjects does not equate to the primary immune response that would be induced by a first, single 10 µg dose with Thomas's vaccine. *See* §III.A.2.a.; EX2026, ¶¶95–97, 102.

Accordingly, a POSA would not have reasonably expected that “explor[ing] across a range of antigen doses” for Thomas's vaccine would have achieved the

claimed seroconversion rates in a population of human subjects after a single dose or prime administration. EX2026, ¶¶102–103.

d. Dr. Guirakhoo cites no evidence establishing that the dose or adjuvant in Thomas’s vaccine would have been a result-effective variable.

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; EX2026, ¶¶104–107. Dr. Guirakhoo merely 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 saw *some* amount of seroconversion after “a dose” of Thomas’s vaccine in a subset of Thomas’s seronegative subjects is insufficient to render the claims obvious. EX2026, ¶¶53–55, 104. Notably, the *rate* of seroconversion that Thomas observed in the population of its study subjects after the first dose was *negligible* and completely in line with other known inactivated flavivirus vaccines that did *not* induce significant seroconversion after a single dose. EX1004, 42:4–20; *see* §II.B.; EX2026, ¶¶53–55, 104. Dr. Guirakhoo’s

allegation, therefore, does not support the notion 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. EX2026, ¶104.

Dr. Guirakhoo, thus, does not establish that the dose and/or adjuvant amount or type are result-effective variables. Such conclusory testimony is entitled to little weight and is not sufficient to support institution. *Xerox Corp. v. Bytemark, Inc.*, IPR2022-00624, Paper 9 at 15 (P.T.A.B. Aug. 24, 2022); *Deeper, UAB v. Vexilar, Inc.*, IPR2018-01310, Paper 7 at 26–27 (P.T.A.B. Jan. 24, 2019); 37 C.F.R. § 42.65(a).

Moreover, Thomas's failure to achieve the claimed seroconversion rates in a population of humans after a single dose or prime administration belies Dr. Guirakhoo's assertion that it would have been easily achieved by simply altering the dose and amount or type of adjuvant. EX2026, ¶¶105–107. Indeed, such a vaccine would have been more attractive than a two-dose ZIKV vaccine, especially for pregnant individuals and travelers. EX2026, ¶¶58, 122.

Yet, Thomas did not achieve a single-dose inactivated ZIKV vaccine. *See* § III.A.1., *supra*; EX2026, ¶¶72–80. Moreover, if Dr. Guirakhoo's allegations regarding routine optimization were correct, then POSAs would have successfully made most, if not all, inactivated flavivirus vaccines into single dose vaccines by

simply increasing the dosage, adjuvant, and/or adjuvant type. EX2026, ¶106. But Dr. Guirakhoo's unsupported conclusion, again, runs contrary to what was known before November 3, 2017, about the seroconversion rates of other inactivated flavivirus vaccines in populations of human subjects not being at least 60% or greater after a single dose when administered. *See* §II.B., *supra*; EX2026, ¶¶53–55, 105–106. It also runs contrary to Martinez's inactivated DENV-1 vaccine that investigated different doses (2.5 µg and 5 µg) and resulted in no difference in seroconversion rates after a single dose (11% and 10%, respectively).¹¹ EX2010, Table 3; EX2026, ¶¶54, 105.

Accordingly, Dr. Guirakhoo fails to demonstrate that a POSA would have been able to routinely optimize Thomas's inactivated ZIKV vaccine to achieve the claimed seroconversion rates in humans that are recited in the Single Dose/Prime Administration Claims. EX2026, ¶¶104–107. And Dr. Guirakhoo, consequently, does not provide any evidence to support his claim that a POSA would have had a reasonable expectation of successfully achieving the seroconversion rates of the

¹¹ As mentioned above, 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; EX2026, ¶54 n.3.

Single Dose/Prime Administration Claims in humans based on Thomas and the prior art. *Id.*

3. Dr. Guirakhoo fails to address other evidence that contradicts his conclusory opinions.

In addition to the foregoing, Dr. Guirakhoo does not address that it would have been well-known to a POSA that inactivated flavivirus vaccines in the art had required two doses to achieve significant seroconversion in a population of human subjects before November 3, 2017. *See* §II.B, *supra*; EX2026, ¶¶53–55, 108–112. Dr. Guirakhoo also conspicuously fails to grapple with Valneva’s own data from its Phase 1 trial of its inactivated ZIKV vaccine. EX2026, ¶¶113–117. As discussed below, that data contradicts his conclusory claim that a POSA would have been able to routinely optimize Thomas’s inactivated ZIKV vaccine to achieve the claimed seroconversion rates of the Single Dose/Prime Administration Claims. EX2026, ¶¶108–117. This further demonstrates the weakness of the merits of Valneva’s challenge to the Single Dose/Prime Administration Claims.

a. Dr. Guirakhoo fails to address the characteristics of known inactivated flavivirus vaccines, which required more than one administration to induce significant seroconversion in a population of human subjects.

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. *See* §II.B., *supra*; EX2026, ¶¶53–55, 109–112. Those vaccines did not

achieve greater than 60% seroconversion in a population of human subjects after a single dose. EX2016, 20; EX2015, Table 2; EX2010, Table 3; EX2017, 1471–1472; EX2026, ¶¶53–55, 110; *see also* §II.B., *supra*.

Dr. Guirakhoo’s assertion that a POSA could have achieved the claimed seroconversion rates in a population of human subjects also runs contrary to Martinez’s inactivated DENV-1 vaccine’s data. Martinez investigated different doses (2.5 µg and 5 µg) that resulted in no difference in seroconversion rates after a single dose (11% (2.5 µg) and 10% (5 µg)). EX2010, Table 3; EX2026, ¶¶53–55, 110. And neither dose of Martinez’s vaccine came close to achieving at least 60% seroconversion in a population of human subjects after a single dose. EX2010, Table 3.

Dr. Guirakhoo does not address those facts that would have been well-known to a POSA. EX2026, ¶¶111–112. In fact, Thomas would have directed a POSA to such information, stating “With the information known about the dosing and schedule for other PIV [purified-inactivated vaccine] flavivirus vaccines – such as Japanese encephalitis and tick-borne encephalitis – someone skilled in this art can determine a safe and effective dose and schedule for this ZIKV PIV.” EX1004, 4:24–28; EX2026, ¶111. Yet, Dr. Guirakhoo does not even acknowledge in his analysis that it was known in the art that dosing schedules and seroconversion rates of greater than 60% in human subjects required at least two

doses for known inactivated flavivirus vaccines. *See, e.g.*, EX1002, ¶¶168–179; EX2026, ¶111. He also fails to provide evidence of any inactivated flavivirus vaccines with single-dose administration schedules for humans in his declaration. *See, e.g.*, EX1002, ¶¶168–179; EX2026, ¶¶108–112.

Overlooking this information further renders weak the merits of Valneva’s Petition because of Valneva’s reliance on Dr. Guirakhoo’s lacking testimony. *Nalox-1 Pharm., LLC v. Opiant Pharm., Inc.*, IPR2019-00699, Paper 13 at 16–19 (P.T.A.B. Oct. 16, 2019) (citing *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1305–06 (Fed. Cir. 2015) (finding that the prior art as whole directed away from the claimed invention); *Nintendo Co., Ltd. v. Genuine Enabling Tech. LLC*, IPR2018-00543, Paper 7 at 21 (P.T.A.B. Aug. 6, 2018) (finding the petitioner had not demonstrated obviousness when the prior art was viewed as whole and petitioner’s expert provided no “reasoned analysis, with record support, that demonstrate[d]” the asserted combination of art would work).

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

Valneva’s own Phase 1 trial of its inactivated ZIKV vaccine further contradicts Dr. Guirakhoo’s conclusory statement that a POSA could have routinely optimized Thomas’s ZIKV vaccine to achieve the claimed seroconversion rates. EX2026, ¶¶113–117. In a Phase 1 trial conducted in 2018,

Petitioner Valneva evaluated two different doses and two different dosing schedules of its inactivated ZIKV vaccine, which was developed on the same platform as the one it used for its JEV vaccine, IXIARO® (discussed in §II.C., *supra*). EX2007, Abstract; EX2026, ¶114. Valneva reported the results in 2022 in Wressnigg. EX2007; EX2026, ¶114. Wressnigg’s data shows that Valneva was not able to achieve the claimed seroconversion rates after a single dose by adjusting the dose and dosing schedule. EX2026, ¶¶113–117.

Valneva investigated its inactivated ZIKV vaccine using a “standard regimen” of two doses at Day 1 and Day 29 and a “rapid regimen” of two doses at Day 1 and Day 7. EX2007, 2; EX2026, ¶115. And each dosing regimen employed two different doses: 3 antigen units (3AU) and 6 antigen units (6AU). EX2007, 2; EX2026, ¶115.

Using a neutralizing antibody titer cut-off of $\geq 1:10$, Valneva did not observe at least 60% seroconversion in the study subjects until after two doses or not at all. EX2007, 3, 6, FIG. 2; EX2026, ¶¶114–116. Wressnigg’s Figure 2 demonstrates that (1) both the 3AU and 6AU “standard regimen” schedules did not induce at least 60% seroconversion until after the second dose, i.e., at Day 35; (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; EX2026, ¶116.

Accordingly, contrary to Dr. Guirakhoo's conclusory argument, adjusting doses (3AU vs. 6AU), as well as adjusting dosing schedules (standard vs. rapid), failed to result in a seroconversion rate of at least 60% after a single dose of Valneva's inactivated ZIKV vaccine in a population of human subjects. EX2007, 6, FIG. 2; EX2026, ¶¶113–117.

As set forth above, Dr. Guirakhoo fails to demonstrate where the claimed seroconversion rates in human subjects are in the prior art (§III.A.1.), he fails to cite any evidence to support his claim that a POSA could have routinely optimized Thomas's inactivated ZIKV vaccine to achieve the claimed rates or that a vaccine's dose or adjuvant are result-effective variables (§III.A.2.), and other prior art inactivated flavivirus vaccines and Valneva's own inactivated ZIKV vaccine data contradict his opinions (§III.A.3.); EX2026, ¶¶70–117.

Valneva's reliance on Dr. Guirakhoo "to fill gaps in the prior art" with conclusory, unsupported testimony renders the merits of its challenge to the Single Dose/Prime Administration Claims weak and demonstrates that Valneva has failed to establish that it is reasonably likely to prevail with respect to its challenge to the Single Dose/Prime Administration Claims. *Xerox* at 15; *Deeper* at 26–27; 37

C.F.R. § 42.65(a); *Bungie, Inc. v. Acceleration Bay, LCC*, IPR2017-01601, Paper 11 at 13 (P.T.A.B. Jan. 9, 2018) (denying institution because the petitioner had not shown that the prior art disclosed all of the limitations of the challenged claims”); 37 C.F.R. § 42.104(b)(4) (requiring Petitioner to “specify where each element of the claim is *found in the prior art*”). And, again, as the “master of its own petition,” Valneva cannot now go back and attempt to fill the holes in its Petition and Dr. Guirakhoo’s testimony. *Qualcomm*, 134 F.4th at 1367.

B. Valneva’s Challenge In Grounds VII–XI Fails To Establish Unpatentability Of The Fetal Protection Claims.

In Grounds VII–XI, Valneva seeks to combine Thomas with one or more of Faucette, Barbero, Murata, and Version 8 of NCT02952833 to challenge the Fetal Protection Claims. Pet., 47–63; EX1002, ¶4.

In doing so, Valneva uses different combinations of prior art for each Ground to support its arguments:

- Ground VII combines Thomas and Faucette;
- Ground VIII combines Thomas, Faucette, and NCT02952833;
- Ground IX combines Thomas, Faucette, and Barbero;
- Ground X combines Thomas, Faucette, NCT02952833, and Barbero;
- and
- Ground XI combines Thomas, Faucette, and Murata.

Pet., 47–63; EX1002, ¶4.

By advancing five different combinations of prior art that do not appear to build on each other, Valneva is essentially proposing that a POSA would have sought five different pathways to arrive at the invention claimed in the '802 patent. EX2026, ¶¶118–125. And in making those five different proposed combinations, Valneva simply sought out where the elements of the challenged claims were found in the applied references and without to regard why the elements would have been chosen by a POSA. *Id.* Indeed, Valneva does not specify why a POSA would have selected certain elements of the Fetal Protection Claims and practice them in the claims as a whole when making Valneva's proposed combinations, as discussed in the sections below. *Id.*, ¶¶118–139.

But, obviousness cannot be based on hindsight, and “a party who petitions the Board for a determination of unpatentability based on obviousness must show that ‘a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention” *NetScout Sys., Inc. v. Longhorn HD LLC*, IPR2021-01258, Paper 11 at 8–9 (P.T.A.B. Feb. 10, 2022) (quoting *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016)); *Grain Processing Corp. v. Am. Maize-Prod. Co.*, 840 F.2d 902, 907 (Fed. Cir. 1988) (“Care must be taken to avoid hindsight reconstruction by using ‘the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit.’”).

1. Valneva fails to establish that a POSA would have sought to practice the Fetal Protection Claims with Thomas’s inactivated ZIKV vaccine.

Valneva challenges the Fetal Protection Claims in Grounds VII–XI by relying on Thomas and Faucette, along with combinations of NCT02952833, Murata, and Barbero. Pet., 47–63; EX1002, ¶¶4; EX2026, ¶¶118–120. Each of the Fetal Protection Claims (claims 9, 32–58, and 64–67) 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; EX2026, ¶120.

To address those claims, Valneva purports to combine Thomas with Faucette. Pet., 47; EX1002, ¶¶397, 465, 483, 513, 522; EX2026, ¶121. Valneva alleges that Thomas discloses a desire to protect both the pregnant woman and their fetuses from a ZIKV infection, and Faucette discloses 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.’” Pet., 50; EX1002, ¶418 (citing EX1007, Abstract, 2549; EX1004 2:13–24, 4:2–7, 18:26–30); EX2026, ¶121.

Yet, Valneva does not explain why a POSA would have had a reason to use Thomas’s vaccine—which required two doses, spread 28 days apart, to induce significant seroconversion in a population of human subjects—to transfer a vaccine effective amount of neutralizing antibodies against ZIKV *to a fetus or newborn.*

See, e.g., Pet., 51–52; EX1002, ¶¶417–419; EX2026, ¶¶122–127. Indeed, a POSA would have been aware that ZIKV infection during pregnancy can have fatal outcomes (such as congenital defects) in fetuses. EX2020, 1982; EX2026, ¶¶57–59, 122. Accordingly, 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. EX2026, ¶58. But, Thomas’s vaccine achieved an insufficient titer of 1:7 28 days after the first dose in humans. EX1004, 42:4-20 (“All” group); EX2026, ¶¶78, 122. Thus, a POSA would not have selected Thomas’s vaccine for rapid onset of immunity during pregnancy.

Moreover, as discussed above in §III.A.2., Thomas’s ZIKV vaccine would not have been reasonably expected to be routinely optimized to achieve significant seroconversion with a single dose or prime administration. EX2026, ¶¶91–101, 123.

In fact, *first*, a POSA would not have relied 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” because that statement was based on data in mice, which is often not predictive of what would happen in humans. EX2021, 835–836; EX2018, 5; EX2026, ¶¶82–84, 124. Moreover, Thomas’s own data in humans provides intrinsic evidence that the

results obtained in mice were not observed in humans. EX1004, 42:4–20; EX2026, ¶¶85–90, 124.

Second, a POSA would have understood that because of the body's primary and anamnestic immune responses, that two 5 µg doses of Thomas's inactivated ZIKV vaccine given several weeks apart could not have been simply changed to a single 10 µg dose and been expected to achieve significant seroconversion in a population of human subjects after a single dose or prime administration. *See* §III.A.2.a., *supra*; EX2026, ¶¶92–98, 125. In other words, a POSA would not have expected a single 10 µg dose of Thomas's inactivated ZIKV vaccine to induce a similar or higher seroconversion rate than that observed with two 5 µg doses administered several weeks apart. *See* §III.A.2.a., *supra*; EX2026, ¶¶92–98, 125.

Third, it was known in the art before November 3, 2017, that other inactivated flavivirus vaccines required at least two doses to induce at least 60% seroconversion in a population of human subjects. EX2016, 20; EX2015, 1331; EX2010, Table 3; EX2017, 1471–1472; EX2026, ¶¶53–55, 126.

And, *lastly*, Dr. Guirakhoo fails to cite to any evidence that one could achieve the claimed seroconversion rates by simply adjusting the dose and/or adjuvant type or adjuvant amount in Thomas's vaccine. *See* §III.A.2.d., *supra*; EX2026, ¶¶104–107, 127. And his claim that one could is contradicted by

Martinez’s inactivated DENV-1 vaccine and Valneva’s own inactivated ZIKV vaccine studies. *See* §III.A.3.; EX2026, ¶¶109–117, 127.

2. Valneva 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.

In Grounds VIII and X, Valneva relies on the inaccurate and unsupported conclusory opinions of Dr. Guirakhoo to allege that a POSA would have combined Thomas, Faucette, and NCT02952833 to arrive at the 10 µg dose recited in claims 34, 43–46, 48, 54, and 64. Pet., 57–59, 60–61; EX1002, ¶¶465–482, 513–521; EX2026, ¶128.

First, Dr. Guirakhoo incorrectly alleges that a POSA would have looked to NCT02952833 when selecting a dose for pregnant women. EX1002, ¶467; EX2026, ¶¶128–133. Dr. Guirakhoo states that a POSA “would have looked to the art for examples of ZPIV [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; EX2026, ¶130. But pregnant women were specifically excluded from the NCT02952833 study, with the study’s inclusion criteria stating,

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, 13; EX2026, ¶130. NCT02952833, therefore, does not indicate that a 10 µg dose would be appropriate for pregnant women. EX2026, ¶130.

Second, Valneva relies on Dr. Guirakhoo's unsupported conclusion that the claimed dose is a result-effective variable affecting seroconversion that could have been routinely optimized. But, as discussed above in §III.A.2., this conclusion is not established or borne out by the prior art. EX2026, ¶¶104–107, 131.

Valneva's choice to combine NCT02952833 with Thomas and Faucette, thus, lies solely on NCT02952833's disclosure of the claimed 10 µg dose that is recited in Claims 34, 43–46, 48, 54, and 64. EX1002, ¶470; EX2026, ¶¶132–133. Indeed, Dr. Guirakhoo's basis for selecting a 10 µg dose for pregnant subjects is Thomas's statement that other inactivated 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; EX2026, ¶¶132–133.

But, again, Dr. Guirakhoo does not cite any evidence to support his claim that adjusting an inactivated ZIKV vaccine's dose would have resulted in the vaccine being able to seroconvert subjects after a single dose. EX2026, ¶133. 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; EX2026, ¶¶53–55, 133. 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; EX2026, ¶¶113–117, 133.

Consequently, a POSA would still not have selected Thomas’s inactivated ZIKV vaccine to vaccinate pregnant human subjects because the POSA would not have expected that simply adjusting the dose of Thomas’s inactivated ZIKV vaccine would result in significant seroconversion after a single dose in human subjects. EX2026, ¶¶72–80, 128–133. 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; EX2026, ¶133.

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

Valneva does not explain or support with evidence why a POSA would have arrived at 200 µg as being a “suitable amount of adjuvant” in Ground X. Pet., 60–61; EX1002, ¶517; EX2026, ¶¶134–139.

In this Ground, Valneva purports to combine Thomas, Faucette, NCT02952833, and Barbero. Pet., 60–61; EX1002, ¶¶513–521. Valneva points to Barbero’s disclosure of using 500 µg of an aluminum hydroxide adjuvant per ml of ZIKV vaccine. Pet., 61, 46; EX1002, ¶517. Valneva then states:

[A] POSA would have been motivated to use the 500 µg [amount of the aluminum hydroxide adjuvant] of Barbero with a reasonable expectation of success because Thomas teaches the use of adjuvants in a suitable amount and the selection of amount of adjuvant is routine optimization of a result-effective variable.

[A] POSA would 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.

Pet., 46; EX1002, ¶517.

Yet, Valneva again relies on Dr. Guirakhoo’s conclusory statement that a POSA would be motivated to choose using 200 µg aluminum hydroxide adjuvant because it is allegedly a “result-effective variable affecting seroconversion.” Pet., 46; EX1002, ¶517; EX2026, ¶¶135–136. But, as discussed above in §III.A., Dr. Guirakhoo’s opinion is unsupported with any cited evidence and does not establish that the amount of adjuvant is a result-effective variable. EX2026, ¶¶91–107, 135–136.

Moreover, as Dr. Guirakhoo points out, 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; EX2026, ¶137. Dr. Guirakhoo does not explain why one would seek to *lower* the amount of adjuvant from Barbero and do that to *positively* affect the seroconversion rate of Thomas’s vaccine. EX2026, ¶137.

Rather, it follows that Dr. Guirakhoo landed on selecting optimizing Thomas’s vaccine to use 200 µg of aluminum hydroxide adjuvant based solely on that amount of adjuvant being recited in the claims challenged in Ground X. EX1002, ¶517; EX2026, ¶138. Indeed, Dr. Guirakhoo’s only basis for selecting the claimed 200 µg of aluminum hydroxide adjuvant is that the amount of adjuvant is allegedly “a routine design parameter,” 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; EX2026, ¶¶137–138. That is, he does not explain how it 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, ¶517; EX2026, ¶¶134–139.

In view of §§III.B.1.–III.B.3., above, Valneva, fails to establish why a POSA would have combined the prior art and seek to practice the elements of the Fetal Protection Claims in each of Grounds VII–XI. EX2026, ¶¶118–139. This failure on Valneva’s part warrants denial of institution. *NetScout* at 8–9.

4. Valneva fails to establish why a POSA would have had a reasonable expectation of success in arriving at the methods of the Fetal Protection Claims.

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. Valneva relies on Dr. Guirakhoo’s conclusory statement that Thomas teaches a successful adoptive transfer in animal studies to support its 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 to the fetus or newborn. Pet., 50–51 (citing EX1002, ¶¶407–411); EX2026, ¶¶140–152.

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

Thomas’s adoptive transfer studies are of experimental animal studies involving *intravenous transfer* of *purified*, vaccine-generated neutralizing

antibodies to *adult non-human recipients*. EX1004, 38:5–16; 38:17–22; 8:24–26; 38:30–39:2; EX2026, ¶¶141–150. They are *not studies of human mother-to-fetus transfer* of a vaccine effective amount of neutralizing antibodies. EX2026, ¶¶141–150. A POSA, therefore, would not have found Thomas’s experimental adoptive transfer studies involving adult non-human recipients to be informative as to what would have reasonably been expected with regard to mother-to-fetal transfer in humans, as the two are largely unrelated processes. *Id.*

As shown in the table below prepared by Dr. Barouch, there are several significant differences between Thomas’s adoptive transfer studies and mother-to-fetus transfer that would have been recognized by a POSA. *Id.* And as the person who conceptualized, designed, performed, and reported the data from Thomas’s adoptive transfer studies, Takeda’s expert Dr. Barouch explains why such differences would have been understood to matter to a POSA. *Id.*

	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)

EX2026, ¶142.

Objective: As Dr. Barouch states, the goal of Thomas’s adoptive transfer studies was to design an innovative laboratory experiment to demonstrate that intravenous injection of purified antibodies from monkeys and humans, in isolation from other immune components, would protect against ZIKV challenge in ZIKV seronegative adult animals. EX1004, 38:5–29, 43:5–10; EX2026, ¶143. A POSA would have understood that the experimental objective of Dr. Barouch and his colleagues was to demonstrate that antibodies could be a correlate of protection against an experimental ZIKV challenge and to define the antibody titer required for protection in adult animal models. EX2004, 1129–1130; EX2026, ¶143. That experimental approach would have been understood by a POSA to be

fundamentally different and not a model for natural human maternal-to-fetal transfer of antibodies across the placental barrier to protect an infant against developing the neurologic consequences of congenital ZIKV syndrome. EX2026, ¶¶143-144.

In fact, by November 3, 2017, congenital ZIKV syndrome was known in the art to involve fetal neurologic developmental birth defects as a result of *in utero* ZIKV infection. EX2031, 1081, 1084; EX2003, 474; EX2020, 1982; EX2026, ¶¶57–58, 144. ZIKV infection *in utero* would have been understood by a POSA to be a very different and more complicated pathogenesis than simply viral replication in peripheral blood following experimental ZIKV challenge of laboratory animals. EX2026, ¶144. Indeed, by November 3, 2017, the art reported that models of ZIKV infection of fetuses showed that fetal infection occurred through transplacental transmission of the virus to the fetus. EX2031, 1082, 1085; EX2033, 1258; EX2026, ¶144. The placenta also showed 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; EX2026, ¶144. The art also reported that ZIKV fetal infection led to cell death in fetal neural tissue and arrested fetal brain growth. EX2032, 270; EX2033, 1257; EX2026, ¶144. In contrast, Thomas’s adoptive transfer studies investigated the ability of ZIKV vaccination to simply prevent ZIKV replication in blood and not

anything to do with investigating the neuropathology of ZIKV infection or how ZIKV leads to neurologic congenital tissue damage the results in birth defects. EX2004, 1130, Figs. 3 and 4; EX2026, ¶144.

Because of these fundamental differences, a POSA would have known that it was not at all clear if the same immunologic mechanisms or antibody titers relevant for protection against viral infection in an adult would have been relevant to the *in utero* setting. EX2026, ¶¶144–145. And those differences would have made the results of Thomas’s adoptive transfer studies not reasonably predictive of successful vaccine protection arising from mother-to-fetus transfer. *Id.*

Antibody Dose/Formulation/Route: Thomas obtained laboratory purified IgG derived from a vaccinated adult human or monkey and administered it by the intravenous route at a fixed dose to a recipient adult animal, i.e., either a mouse or a monkey. EX1004, 38:5–29, 43:5–10; EX2004, 1129–30; EX2026, ¶146. The purified IgG, therefore, was directly released into the peripheral bloodstream, where it could start to neutralize the ZIKV directly in the host’s bloodstream. EX2041, 543; EX2026, ¶146. 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; EX2026, ¶146. Indeed, a POSA would have known that the presence of inflammatory cytokines, innate

mediators, and other plasma components can affect the functions of antibodies.

EX2038, Abstract, 84; EX2042, Abstract, 5; EX2026, ¶146. Those major differences in the antibody dose, format, and route also make the results of Thomas's adoptive transfer studies not reasonably predictive of successful vaccine protection arising from mother-to-fetus transfer. EX2026, ¶146.

ZIKV Dose/Formulation/Route: In Thomas's adoptive transfer studies the dose administered to the animal recipients was given intravenously or subcutaneously. EX1004, 38:5–29, 43:5–10; EX2004, 1129–30; EX2026, ¶147. Thomas's studies utilized a high-dose ZIKV challenge that was not physiological in relation to the natural amount ZIKV that would enter a subject through a mosquito bite. EX1004, 38:5–29, 43:5–10; EX2004, 1129–30; EX2026, ¶147. And, as discussed above, Thomas investigated protection against that high dose using purified IgG, directly released into the peripheral bloodstream, where it could start to neutralize the ZIKV directly in the host's bloodstream. EX2026, ¶147.

A POSA would have understood that such an experimental system would not have been informative for mother-to-fetal transfer given that (1) the different pathology of fetal ZIKV infection, discussed above; and (2) the dose of ZIKV a fetus receives from the placental transfer of the virus from an infected mother, and what immune response would be needed to protect against that dose, was

unknown. EX2040, 6-7, 9; EX2026, ¶148. 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. EX2026, ¶¶147–148.

Donor/Recipient: In Thomas's adoptive transfer studies the donor was a vaccinated adult human or monkey, and the recipients were adult mice or monkeys. EX1004, 38:5–29, 43:5–10; EX2004, 1129–30; EX2026, ¶¶142, 149. The Fetal Protection Claims involve the donor being a pregnant human woman, and the recipient is her human fetus receiving the antibodies from transplacental transfer. EX2026, ¶¶39, 120, 149.

As discussed, mice often do not provide immunological responses that are predictive of human responses. *See* §§III.A.1.b. and III.A.2.b., *supra*; EX2026, ¶¶82–84, 99–101, 149. 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; EX2026, ¶149. Consequently, a POSA would have understood that Thomas's adoptive transfer studies would not have been reasonably predictive of successful vaccine protection arising from mother-to-fetus transfer. EX2026, ¶149.

In view of the differences outlined above, a POSA would not have concluded that the results of Thomas's adoptive transfer studies would have

provided a reasonable expectation of success of protection arising from mother-to-fetus transfer of neutralizing antibodies. *Id.*, ¶¶140–150. Preventing viral replication following an experimental ZIKV challenge of an adult animal following intravenous adoptive transfer of purified IgG would have been understood by a POSA to be fundamentally different and simpler than seeking to prevent neurologic birth defects following a natural *in utero* infection in a fetus following mother-to-infant transplacental transfer of both neutralizing antibodies and plasma. *Id.*

b. Dr. Guirakhoo cites no evidence supporting that a POSA would have reasonably expected to achieve transferring a vaccine effective amount of neutralizing antibodies from a human mother to the fetus.

Valneva and Dr. Guirakhoo, furthermore, do not provide any evidence to support that a POSA would have reasonably expected achieving transfer of a vaccine effective amount of neutralizing antibodies to the fetus based on Faucette. EX2026, ¶151. While Dr. Guirakhoo points to Faucette for allegedly “acknowledg[ing] that inactivated virus vaccines have successfully been used to immunize pregnant women,” EX1002, ¶419 (citing EX1007, 2549), that disclosure of Faucette provides nothing about how to go about successfully providing a fetus a vaccine effective amount of neutralizing antibodies so as to protect against an *in utero* ZIKV infection. EX1007, 2549; EX2026, ¶151.

Thus, Valneva and Dr. Guirakhoo have not established 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. EX2026, ¶¶140–152. This failure on Valneva’s part also demonstrates that Valneva has not demonstrated that it is reasonably likely to prevail with respect to its challenge. *Triller Inc. v. Tiktok PTE Ltd.*, IPR2022-00181, Paper 9 at 28 (P.T.A.B. May 16, 2022) (denying institution because “Petitioner provides no evidence that an ordinary artisan would have had a reasonable expectation of success.”).

IV. CONCLUSION

In sum, Valneva has not established that it is reasonably likely to prevail with respect to any challenged claim. The Petition’s grounds are legally and substantively flawed, including extensively relying on conclusory testimony from Valneva’s declarant and misapplying the prior art. Institution should be denied.

Respectfully submitted,

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CERTIFICATE OF WORD COUNT (37 C.F.R. § 42.24(d))

1. This Patent Owner's Preliminary Response Under 37 C.F.R. § 42.107 complies with the type-volume limitation of 14,000 words, comprising 13,965 words, excluding the parts exempted by 37 C.F.R. § 42.24(a)(1).

2. This Patent Owner's Preliminary Response Under 37 C.F.R. § 42.107 complies with the general format requirements of 37 C.F.R. § 42.6(a) and has been prepared using Microsoft® Word 2016 in 14-point Times New Roman font.

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CERTIFICATE OF SERVICE (37 C.F.R. § 42.6(e))

I certify that the above-captioned **PATENT OWNER'S PRELIMINARY RESPONSE UNDER 37 C.F.R. § 42.107** and associated Exhibits 2026–2043 were served in their entireties on July 18, 2025, upon the following parties via electronic mail:

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