valneva

A LEADING SPECIALTY VACCINE COMPANY

INVESTOR DAY

NEW YORK, DECEMBER 6, 2022

Today's Agenda

Welcome and Introduction	**Joshua Drumm, Ph.D.** *VP Global Investor Relations*
Company Overview & Pipeline	**Thomas Lingelbach** *Chief Executive Officer*
Chikungunya Vaccine Candidate	**Katrin Dubischar** *VP, Chikungunya Program Director*
Commercial Prospects: VLA1553	**John Kanaras** *VP, General Manager Valneva USA*
Lyme Disease Vaccine Program	**Thomas Lingelbach** *Chief Executive Officer*

Today's Agenda - Continued

Future Clinical Pipeline Overview	**Thomas Lingelbach** *Chief Executive Officer*
Select Pre-Clinical Programs	**Anders Lilja, Ph.D.** *Director, Preclinical R&D*
Commercial Products Portfolio	**Peter Bühler** *Chief Financial Officer*
Financial Overview & Guidance	**Peter Bühler** *Chief Financial Officer*
Q&A – Live and Virtual	**Speaker Panel**
Closing Remarks	**Thomas Lingelbach** *Chief Executive Officer*

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This presentation presents information about VLA1553, an investigational vaccine candidate that has not been approved for use and has not been determined by any regulatory authority to be safe or effective.

Company Overview and Pipeline

Thomas Lingelbach

Valneva Summary and Core Strengths

Fully integrated specialty vaccine company focused on development and commercialization of **prophylactic vaccines for infectious diseases** with significant unmet medical need

- **Highly specialized and targeted approach to development of unique prophylactic vaccines**
- **Advanced pipeline of differentiated clinical-stage assets** designed to address large populations
- **Highly experienced leadership team with vaccine development and regulatory expertise;** clear demonstrated ability of rapidly moving new vaccines through the clinic to commercialization
- **Highly developed, nimble and sophisticated manufacturing infrastructure**
- **Specialist sales infrastructure: three commercialized vaccines; distribution rights for third-party vaccines**

Delivering on Valneva's Value Proposition

Sharpening focus on investments that will create value for the Company

Continue progressing Valneva's advanced programs	Progress new candidates from pre-clinical to clinical stage	Maximize value from commercial products	Re-size operations
▪ Prepare for the potential launch of chikungunya vaccine candidate in the U.S. ▪ Support Pfizer in progressing Lyme	▪ Advance promising early-stage candidates ▪ Evaluate assets for potential in-licensing	▪ Profit from resurging travel ▪ Increase contribution from further 3rd-party distribution deals ▪ Sell available COVID-19 vaccine doses	▪ Reduction of approximately 20 to 25% of its existing workforce ▪ Expected savings of approximately €12 million annually expected

Delivering Value From Advanced Clinical Pipeline and Commercialized Products[1]

[1]As of June 24, 2022, VLA2001 has received emergency use authorization in Bahrain and in the United Arab Emirates, as well as Conditional Marketing Authorization in the UK and standard marketing authorization in Europe.[2] VLA1553 received Fast Track designation from the FDA, PRIME designation from the European Medicines Agency and is also potentially eligible for a U.S. Priority Review Voucher. [3] VLA15 received Fast Track designation from the FDA [4] Indications differ by country - Please refer to Product / Prescribing Information (PI) / Medication Guide approved in your respective countries for complete information, incl. dosing, safety and age groups in which this vaccine is licensed, ETEC = Enterotoxigenic Escherichia coli (E. Coli) bacterium

Chikungunya Vaccine Candidate – VLA1553*

Katrin Dubischar

*VLA1553 is an investigational chikungunya vaccine candidate and is not approved for use in the United States or any other jurisdiction

Chikungunya: A Major Public Health Threat

Mosquito-transmitted disease with potentially debilitating consequences

Aedes aegypti

Aedes albopictus

- Chikungunya virus (CHIKV) is transmitted by ***Aedes*** mosquitoes[1]
- Acute chikungunya, seen in up to 97% of those infected, typically presents with sudden onset of **high fever and joint pain**.[1]
- Often causes **large, explosive outbreaks**, affecting one-third to three-quarters of the population[1]; difficult to predict next outbreaks[2]
- High burden of disease: outbreaks can have substantial health-economic impact; infection can progress to **severe chronic symptoms** in many patients[4]
- **Outbreaks** have occurred in Asia, Africa and across Latin America[1] with the potential for it to happen in the U.S. and Europe[2,4]
- **Returning infected travelers** can trigger local transmission in areas where relevant mosquitoes are established (e.g. Southern U.S./Europe)[2]

No curative treatment and no vaccines available to date

1. Staples et al. CDC Yellow Book 2020, Chapter 4 . 2. Bettis et al, PLOS Neglected Tropical Diseases 16(1): e0010069. 3. Lindsey et al *Am J Trop Med Hyg*. 2018;98(1):192-197. doi:10.4269/ajtmh.17-0668 4. Silva LA et al. J Clin Invest. 2017 Mar 1;127(3):737-749.

VLA1553 at a Glance

Live-attenuated CHIKV vaccine candidate targeting long-lasting immunity with a single shot

CHIKV Vaccine Candidate VLA1553

- **Live-attenuated**, **single** dose, i.m., **lyophilized**
- Based on **La Reunion strain** of East Central South African genotype
- **Attenuation by reverse genetics,** 60aa deletion within the non-structural nsP3 protein

Development Status – Completed Phase 3

- **Pivotal** Phase 3 Trial: **Primary Endpoint (Seroresponse Rate) met**
- **Lot-to-Lot consistency** Trial: **Primary Endpoint met**
- Antibody persistence trial ongoing
- Adolescents trial in Brazil ongoing

Regulatory Milestones

- Biologics licence application (BLA) **rolling submission initiated** in August 2022
- FDA: **Fast Track and Breakthrough designations granted**
- EMA: **PRIME** designation 2020

Target Populations & Geographic Reach

- **Non-endemic** countries: Travelers / Military / Outbreak preparedness in U.S., EU, CAN
- **Endemic** use: Partnered with CEPI and Instituto Butantan, technology transfer

Licensure Pathway for Chikungunya Vaccines

Accelerated approval pathway agreed with regulators for chikungunya vaccines

Classical efficacy studies for chikungunya vaccines are considered unfeasible[1,2]

- Unpredictable and short-lived outbreaks
- Logistical boundaries
- Acceptable timeframes and cost barriers

In the U.S., chikungunya vaccines can be licensed following the "accelerated approval" pathway

- Other regulators also agreed to licensure based on serological endpoints

FDA-agreed surrogate endpoint: "Seroresponse Rate"

1 VRBPAC Meeting, Nov 2019. 2 Bettis et al, PLoS Negl Trop Dis 16(1): e0010069

Overview of Clinical Studies

Three clinical trials completed

Phase 1

- **Phase 1 study[1]:**
  - **120 healthy adults** aged 18-45 years
  - **Three dose levels** of vaccine studied
  - Included a **re-vaccination** as homologous viral challenge
- **Results**
  - **Highly immunogenic after single vaccination**
  - **No anamnestic response or viremia** upon re-vaccination
  - Safety profile **supported Phase 3 progression** with medium dose

Phase 3

- **Pivotal Phase 3 study:**
  - **4,115 participants** aged ≥18 years
  - Randomized, controlled trial comparing **VLA1553 to placebo**
  - Generated **safety and immunogenicity** data
- **Lot-to-lot consistency study:**
  - **408 participants** aged **18-45 years**
  - Randomized, controlled trial comparing **three lots of VLA1553**

Defining the surrogate of protection:

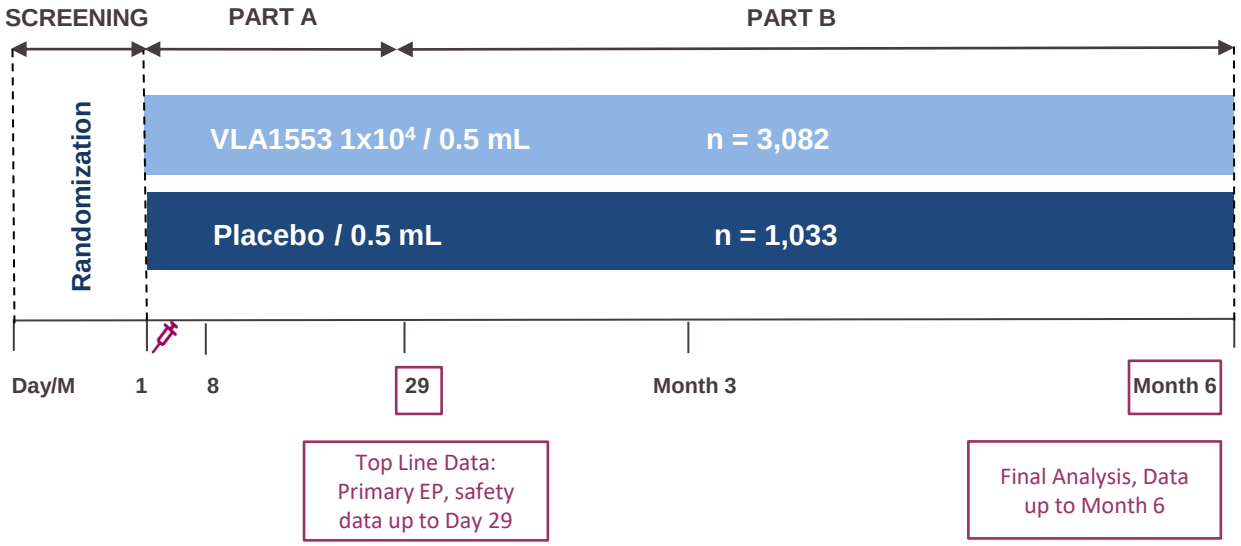
- Human Phase 1 sera protected non-human primates (NHPs) in passive transfer model[2]
- Determined pre-challenge titer resulting in sterilizing immunity in NHPs: seroresponse defined as $\mu PRNT_{50} \geq 150$

1 Wressnigg et al. 2020; Lancet Infect Dis 20:1193-1203.
2 Roques P, et al. 2022; JCI Insight. Jul 22;7(14)

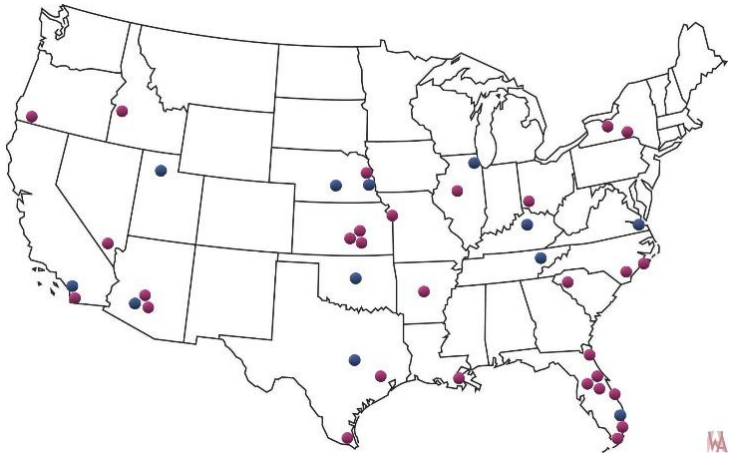
Pivotal Trial Design: VLA1553-301

Multicenter, randomized, placebo-controlled double-blind trial in 4,115 adults

- Primary Endpoint: Proportion of participants with seroresponse (CHIKV neutralizing antibody titer ≥150 by μPRNT$_{50}$) for baseline negative participants 28 days post-vaccination
- 3:1 randomization to VLA1553 and Placebo
- Recruitment stratified by age, younger (18-64 years, N=3,652) and older adults (≥65 years, N=463)
- Immunogenicity subset: first 462 participants enrolled at selected sites
- Solicited adverse events captured for 10 days following vaccination



n = number of participants in the safety population



Blue = Immunogenicity sites
Purple = Non-Immunogenicity sites
(i.e. not enrolling participants within the immunogenicity subset)

High Seroresponse Rate Confirmed in Older Participants

Additional Data in Adults ≥65 Years

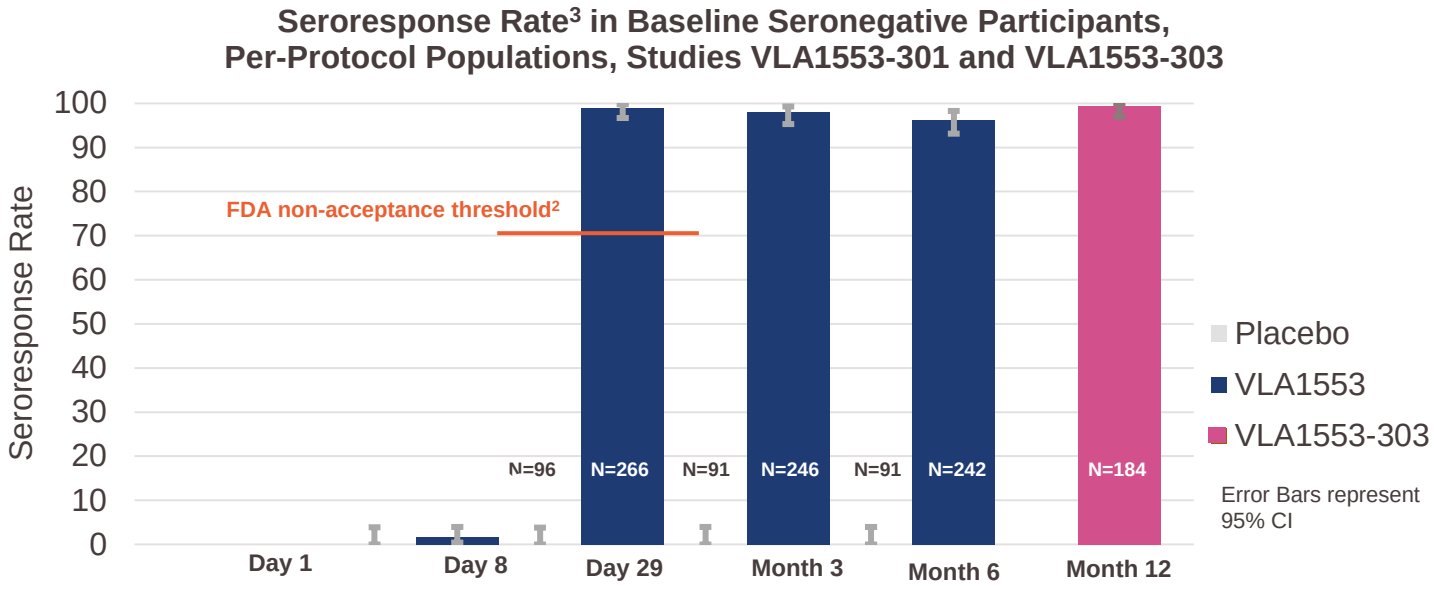
Subjects with Seroresponse	18-64 years VLA1553 N=269	18-64 years Placebo N=94	≥ 65 years VLA1553 N=107	≥ 65 years Placebo N=33
Day 29[a] n (%)	251 **248 (98.8)**	88 **1 (1.1)**	104 **103 (99.0)**	33 **0**
Day 180[a] n (%)	241 **233 (96.7)**	87 **2 (2.3)**	104 **99 (95.2)**	33 **0**

- **107 participants aged ≥65 years were included in a secondary analysis population**
- **Day 29 Seroresponse rate:**
  - **99.0% (103/104, 95% CI: 94.8 – 100.0)**
- **High rate maintained after six months at 95.2% (99/104, 95%CI: 89.1 - 98.4)**

a. Number of µPRNT baseline negative (<20) subjects with non-missing titers at the specified time point.
Percentages are based on the number of subjects with non-missing titers at the visit.
Seroresponse is defined as $\mu PRNT_{50} \geq 150$ for µPRNT baseline negative (<20) subjects.

Seroresponse[1] in 99% of Participants, Retained After 12 Months

12-month persistence data from a subset of pivotal trial confirm earlier findings[2]

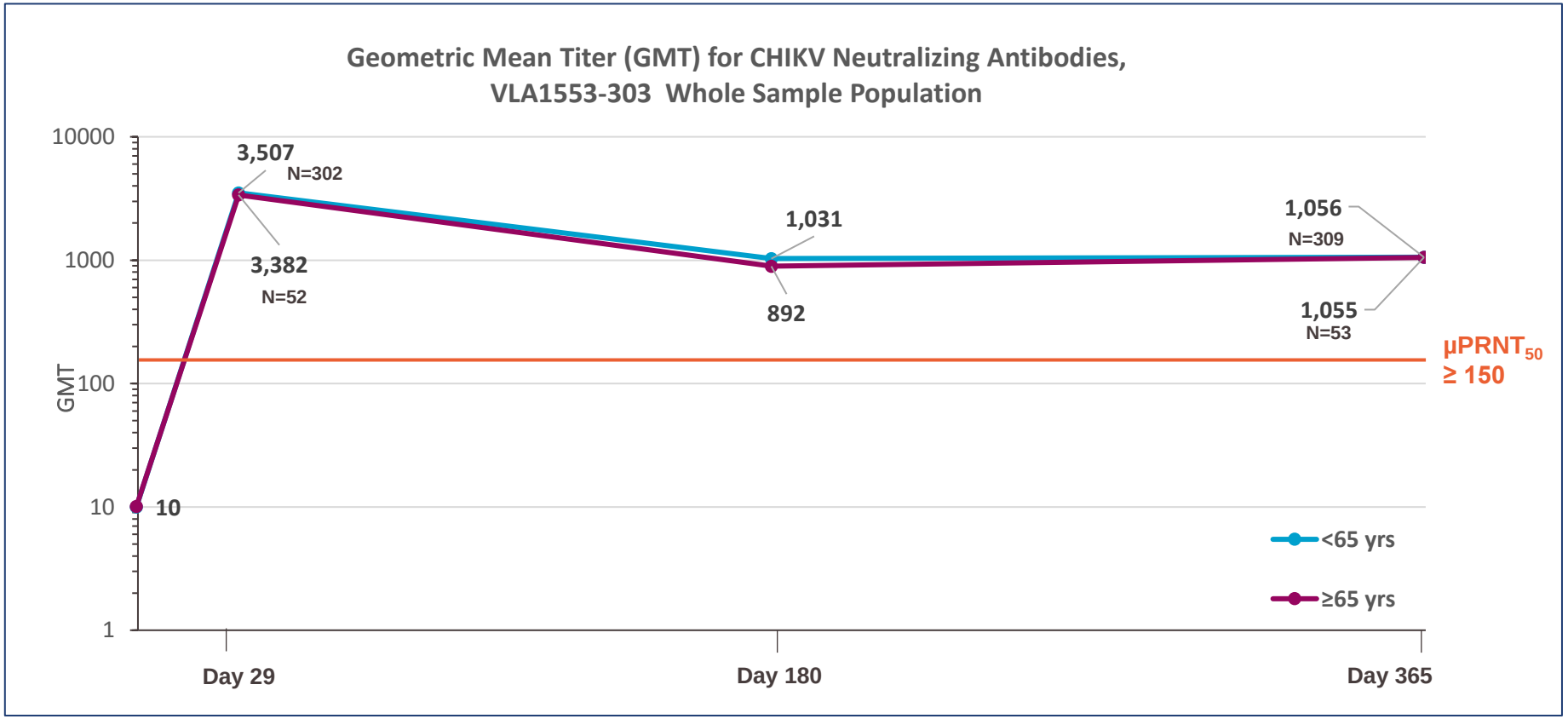


- **Day 29 Seroresponse rate (SRR):**
  - **98.9% (263/266, 95% CI: 96.7- 99.8) vs placebo 0% (0/96, 95% CI 0.0 - 3.8)**
- **High SRR 12 months after vaccination at 99.5% (183/184, 95% CI: 97 – 100)**

1 CHIKV neutralizing antibody titer ≥150 by μPRNT$_{50}$; 2 Wressnigg et al, Lancet ID 20202; 3 The proportion of participants with seroresponse, determined by μPRNT$_{50}$ for baseline negative participants 28 days post-vaccination; 3 The lower bound of the 95% Confidence Interval for the SRR at Day 29 in the VLA1553 group needed to exceed 70%

Stable Neutralizing Antibodies During Follow-up Phase (VLA1553-303)

Comparable titers in participants 18-64 or ≥65 years throughout study



Lot-to-Lot Consistency Study (VLA1553-302)

Immunogenicity profile consistent with pivotal study

Study Design:

- Multicenter, randomized, double-blind Phase 3 trial in 408 adults, aged 18 to 45 years, conducted in U.S.
- Primary Endpoint: Geometric mean titer (GMT) for CHIKV neutralizing antibodies on Day 29 post-vaccination

Results:

- **Lot-to-Lot consistency demonstrated**. GMT Ratio CI's within the defined acceptance margins of 0.67 and 1.5
- **Seroresponse[1] in 97.8% of participants** 28 days after a single vaccination and 96.0% at Day 180

	Lot 1 N=122	Lot 2 N=118	Lot 3 N=122
Day 29 Geometric Mean Titer	**2556.7**	**2767.7**	**2613.7**
95% CI for GM	[2056, 3180]	[2310, 3316]	[2128, 3210]

1 CHIKV neutralizing antibody titer ≥150 determined by µPRNT$_{50}$ for baseline negative participants

VLA1553: Clinical Data Highlights[1,2]

Live-Attenuated CHIKV Vaccine Candidate Targeting Long-Lasting Immunity with a Single Shot

Immunogenicity Data

- Seroresponse[3] Rate (SRR) in 99% of participants after a single vaccination
- Immunogenicity profile maintained over time: 99% SRR after 12 months[4]
- Older adults (≥ 65 years) achieved similar SRR and neutralizing antibody titers as younger adults (<65 years)[1,4]
- 100% seroconversion after 14 days and sustained to Month 12 in preceding trial[2]

Safety Data[1]

- VLA1553 was generally well tolerated among the 3,082 subjects evaluated for safety
- Approximately 50% of study participants experienced solicited systemic adverse events, most commonly headache, fatigue and myalgia
- Majority of solicited adverse events mild or moderate. 2.0% of study participants reported severe solicited adverse events, most commonly fever.

1 Valneva Successfully Completes Pivotal Phase 3 Trial of Single-Shot Chikungunya Vaccine Candidate. **2** Wressnigg et al, Lancet ID: https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30238-3/fulltext; **3** CHIKV neutralizing antibody titer of ≥150 by $\mu PRNT_{50}$ (Micro Plaque Reduction Neutralization Test), agreed with regulators to be used as a surrogate endpoint in Phase 3; 4 Valneva Reports Positive 12-Month Antibody Persistence Data for Single-Shot Chikungunya Vaccine Candidate

VLA1553 Partnerships and Non-Dilutive Funding

Collaboration with CEPI and Instituto Butantan to enhance accessibility

July 2019: Coalition for Epidemic Preparedness Innovations (CEPI) funding

- CEPI provides funding for late-stage development of a single-dose chikungunya vaccine, with support from the European Union's Horizon 2020 program

January 2021: Instituto Butantan, agreement for the development, manufacturing and marketing of VLA1553 in Low and Middle Income Countries (LMICs)

- Valneva will transfer its chikungunya vaccine technology to Instituto Butantan
- In addition to providing commercial access to LMICs, Instituto Butantan will provide certain clinical and Phase 4 studies that Valneva will use to meet additional regulatory requirements in developed markets

*VLA1553 is an investigational chikungunya vaccine candidate and is not approved for use in the United States or any other jurisdiction

VLA1553 Development Outlook

First and only program to meet its Phase 3 trial endpoint worldwide

Completed pivotal clinical trials

- Met all Phase 3 immunogenicity and safety endpoints
- Results confirmed by final lot-to-lot consistency trial results (VLA1553-302)

Additional studies initiated

- Antibody persistence follow-up trial (VLA1553-303) fully enrolled: 363 volunteers from VLA1553-301 will continue to be followed annually for at least five years
- Adolescent Phase 3 trial initiated in January 2022 to support potential label expansion and licensure in Brazil, funded by CEPI; Data expected in 2023

Anticipated future trials

- Co-vaccination, pediatric and special populations, Phase 4 observational effectiveness trial

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VLA1553 Regulatory Outlook

First and only program to initiate regulatory process

Rolling biologics license application (BLA) with FDA commenced in August 2022

- Expect to complete submission by year end 2022; Eligible for priority review request
- Upon BLA acceptance, FDA will determine priority review eligibility and PDUFA date
- Potential VRBPAC meeting - timing will depend on action due date

The sponsor of the first chikungunya vaccine approved in the U.S. will be eligible to receive a Priority Review Voucher[1]

- Company intends to monetize upon receipt; PRVs recently selling for ~$110 million[2]

FDA regulatory designations	EMA regulatory designation
▪ Fast Track (2018) ▪ Breakthrough Therapy (2021)	▪ PRIority MEdicine (PRIME) (2020)

Expect to commence other regulatory processes in H2 2023, incl. EMA

1 https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/tropical-disease-priority-review-voucher-program; 2 https://investors.biomarin.com/2022-02-09-BioMarin-Sells-Priority-Review-Voucher-for-110-Million, https://bridgebio.com/news/bridgebio-pharma-sells-rare-pediatric-disease-priority-review-voucher-for-110-million-and-defers-principal-payment-on-senior-debt-by-two-years/

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Chikungunya Vaccine Candidate – Commercial Outlook

John Kanaras

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Chikungunya - An Emerging Global Health Threat

GLOBAL ARBOVIRUS INITIATIVE

Launch of the Global Arbovirus Initiative

31 March 2022 13:00 – 14:30 CET

The World Health Organization is pleased to announce the launch of the Global Arbovirus Initiative on 31 March at 13:00 Central European Time.

Arthropod-Borne viruses (Arboviruses) such as Dengue, Yellow fever, Chikungunya and Zika viruses are all current public health threats in tropical and sub-tropical areas where approximately 3.9 billion people live. The frequency and magnitude of outbreaks of these arboviruses, particularly those transmitted by *Aedes* mosquitoes, are increasing globally, fueled by the convergence of ecologic, economic, and social factors.

The Global Arbovirus Initiative is an integrated strategic plan to tackle emerging and re-emerging arboviruses with epidemic and pandemic potential focusing on monitoring risk, pandemic prevention, preparedness, detection and response, and building a coalition of partners. The initiative is a collaborative effort between the World Health Emergencies Programme, the Department of Control of Neglected Tropical Diseases, and the Immunization, Vaccines and Biologicals Department.

This integrated initiative will build a coalition of key partners to strengthen the coordination, communication, capacity-building, research, preparedness, and response necessary to mitigate the growing risk of epidemics due to these diseases.

- **WHO recognizes the global public health threat posed by chikungunya and other arthropod-borne diseases**
- **The frequency and magnitude of outbreaks are increasing globally – leading to epidemic and pandemic potential**
- **Returning infected travelers are a primary source of introduction to new geographies**

Source: WHO

Chikungunya has two distinct phases, with the chronic phase lasting for months to years

Chikungunya means “to become contorted” in Kimakonde, describing sufferers’ stooped appearance

Acute Phase (up to 97%)[1]

- Symptoms typically begin 3-7 days after being bitten by an infected mosquito[1]
  - **Fever and joint pain** / joint inflammation, other systemic manifestations[1-4]
  - **Joint symptoms are typically severe and can be debilitating[1]**
- Viremic for 5-10 days[2,3]
- Acute symptoms typically resolve in 7-10 days[1]
- Sub-acute post-viremic state (6-21 days) can occur[3,4]
  - Persistent articular symptoms
  - Tenosynovitis and bursitis

Chronic Phase (~43%)[9]

- **Pattern similar to rheumatoid arthritis**
  - Characterized by peripheral spondylarthritis, undifferentiated arthritis, fibromyalgia, neuropathic chronic pain
- **Fatigue** is another main persistent symptom, can last for months to years[7,8]
- Risk factors for developing chronic symptoms:[(6,9)]
  - >45 years of age
  - Chronic medical condition
  - Newborns infected around time of birth
  - High viral load during acute phase
  - Severe immunologic response in post-viremic phase
- **Chronic disease negatively impacts quality of life and ability to work**

1. Staples et al. CDC Yellow Book 2020, Chapter 4. 2. Rudolph KE, et al. Am J Trop Med Hyg. 2014;90:882-891. 3 Suhrbier A et al. Nat Rev Rheumatol. 2012;8:420-429. 4. Stalkowsky F et al. PLoS one 2009;4:e7603-e7603. 5. Rodríguez-Morales AJ et al . Arthritis Care Res 2016;68:849-58 6. Badawi, et al Int J Infect Dis 67: 107-113. doi:10.1016/j.ijid.2017.12.018 7. Manimunda SP, et al. Trans R Soc Trop Med Hyg 2010; 104: 392–99. 8. Soumahoro MK, et al. PLoS One 2009;4:e7800. 9. Zaid A et al. Arthritis Rheumatol 2018;70:484-95 9. Paixão, E. S. et al. doi:https://doi.org/10.1093/trstmh/try063. 10. Zaid, A. et al. Arthritis Reumatol 70: 484-495. doi:10.1002/art.40403

The Economic Burden Of CHIKV in the Americas Has Been Estimated at $185B

Impact of the 2013-2015 outbreaks – A modelling study

- **The global burden of chikungunya is unknown, but one study estimated the health and cost impact of the 2013–2015 CHIKV epidemic in the Americas.**
- **The study modelled the acute and long-term impact of chikungunya in the Americas from a societal perspective (accounting for both direct and indirect costs and health outcomes).**

39.9 million
Total estimated cases in the Americas

23.8 **Million** disability adjusted life years (DALYs)

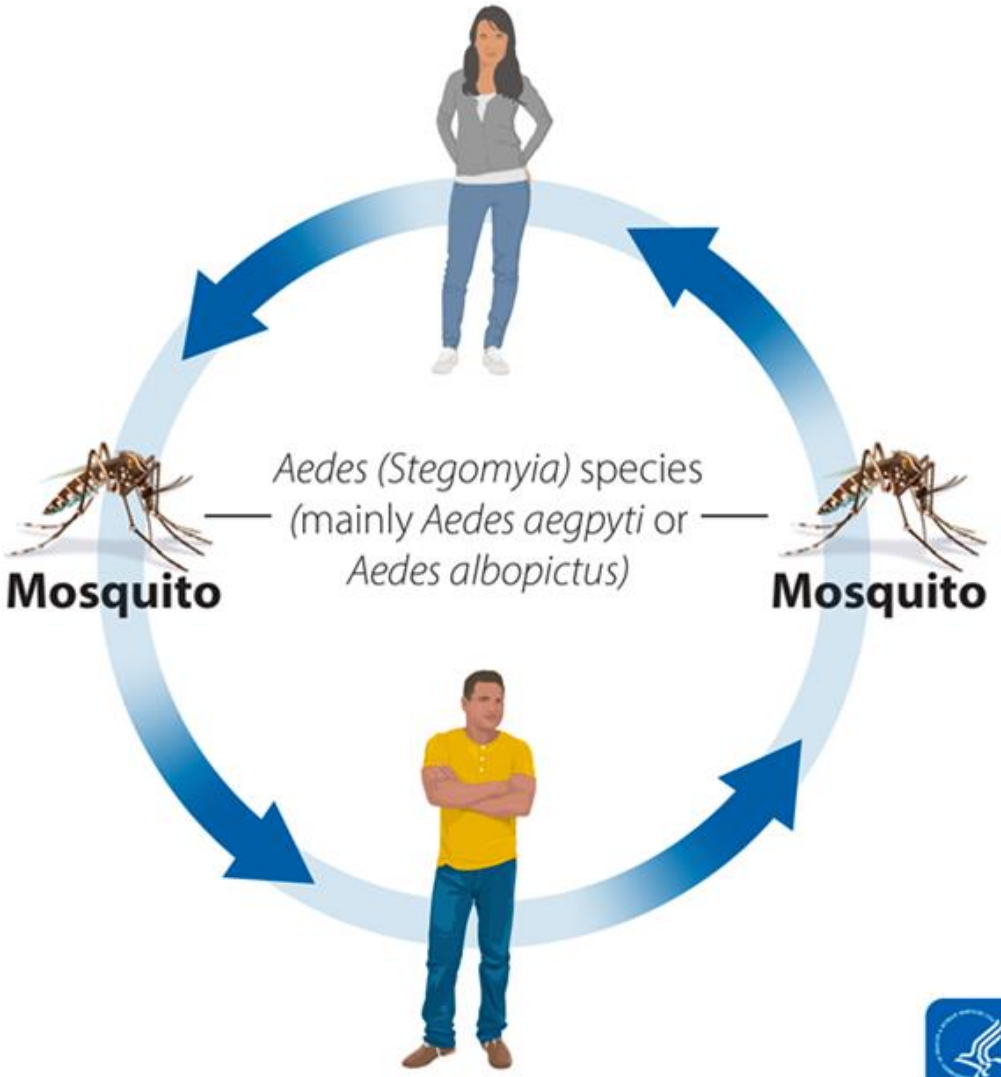
$185 billion USD in costs from a societal perspective **$185B**

- **Chronic inflammatory rheumatism was the source of the vast majority of cost and DALYs lost.**

Bloch, Danielle, "The Cost And Burden Of Chikungunya In The Americas" (2016). Public Health Theses. 1022. https://elischolar.library.yale.edu/ysphtdl/1022

The Urban Transmission Cycle Relies On Both Mosquito Vectors And Humans

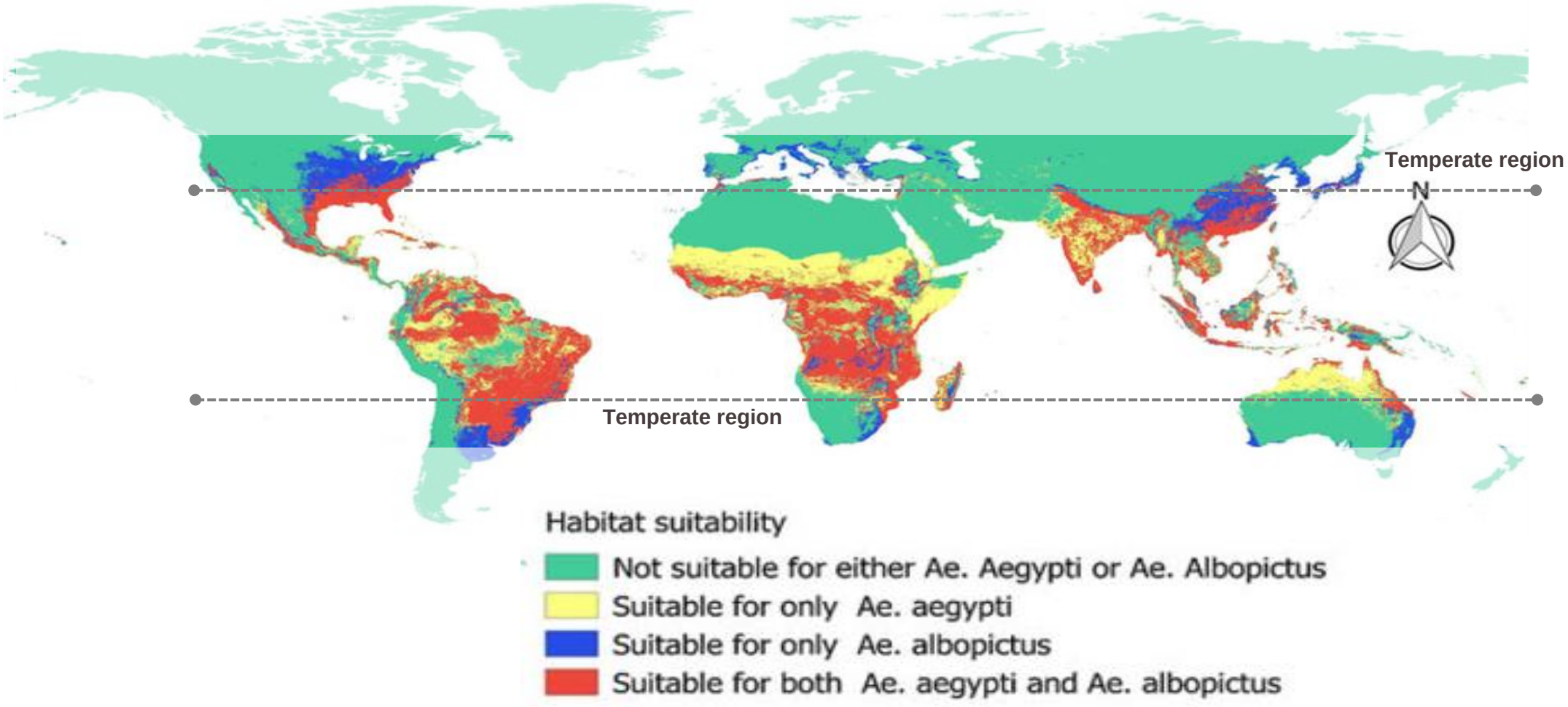
The primary vectors of CHIKV are *Aedes aegypti* and *Aedes albopictus* mosquitoes



Source: https://www.cdc.gov/chikungunya/transmission

The Habitat for The Vectors has Expanded Significantly

Numerous factors have contributed to this geographic expansion

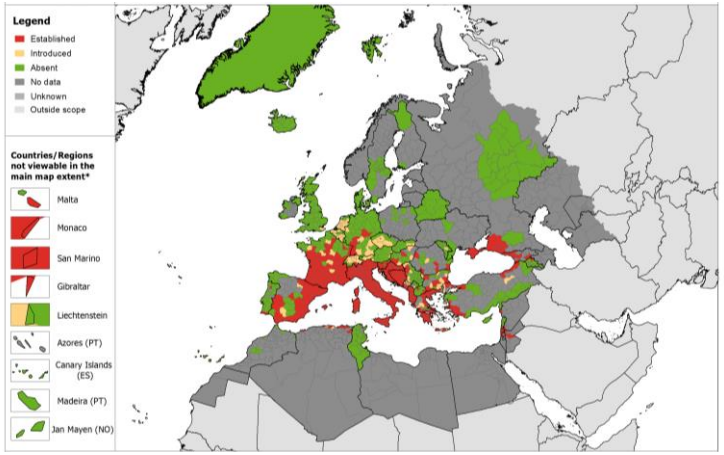


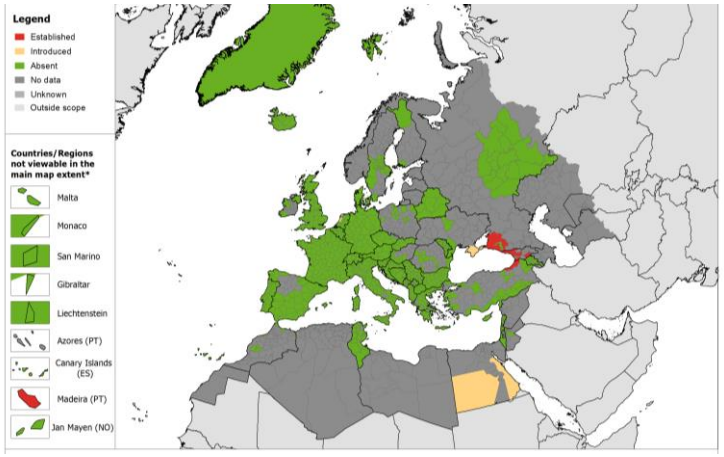
1. Leta, S et al. *Int J Infect Dis* 2018; 67:25-35. 2. Tsetsarkin KA, Vanlandingham DL, McGee CE, Higgs S. *PLoS Pathog*. 2007. 3(12):e201. 3. Nasci RS. *Emerg Infect Dis*. 2014. 20(8):1394-5.

The Aedes Vectors are Now Endemic to Parts of The US and EU

Creating an environment for potential introductions of CHIKV

Estimated Potential Range of *A. albopictus (top) and A. aegypti (bottom)*



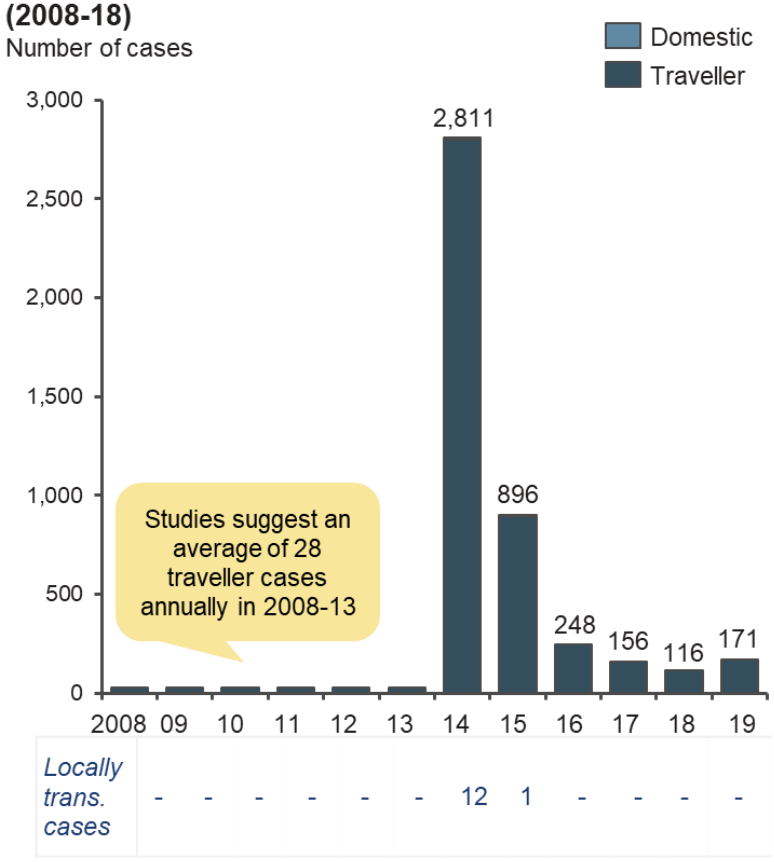


Source: CDC (2017), ECDC (2022)

Imported Cases of Chikungunya are a Key Risk for Local Outbreaks

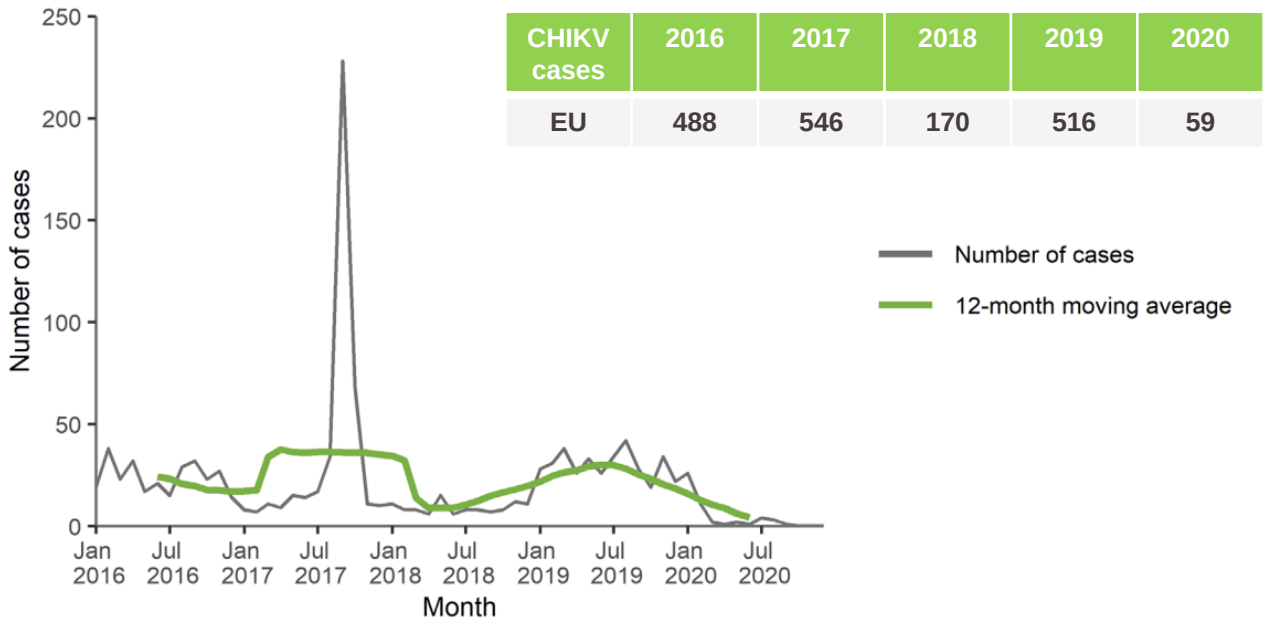
Prior to 2020, there was a steady trend of imported cases of CHIKV in the US and EU

Total confirmed chikungunya cases in the U.S.* (2008-18)



Distribution of chikungunya virus disease cases by month, EU/EEA, 2016–2020

CHIKV cases	2016	2017	2018	2019	2020
EU	488	546	170	516	59



Source: Country reports from Austria, Croatia, Czechia, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Malta, the Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain and Sweden

Sources: CDC, ECDC

Chikungunya Global Market Segments

Global Market for Chikungunya Vaccines Estimated to Exceed $500 Million per Year by 2032[1]

Segments Targeted Directly by Valneva

Travelers from Non-Endemic Regions

Travel vaccine for individuals travelling to areas with risk of chikungunya

Military from Non-Endemic Regions

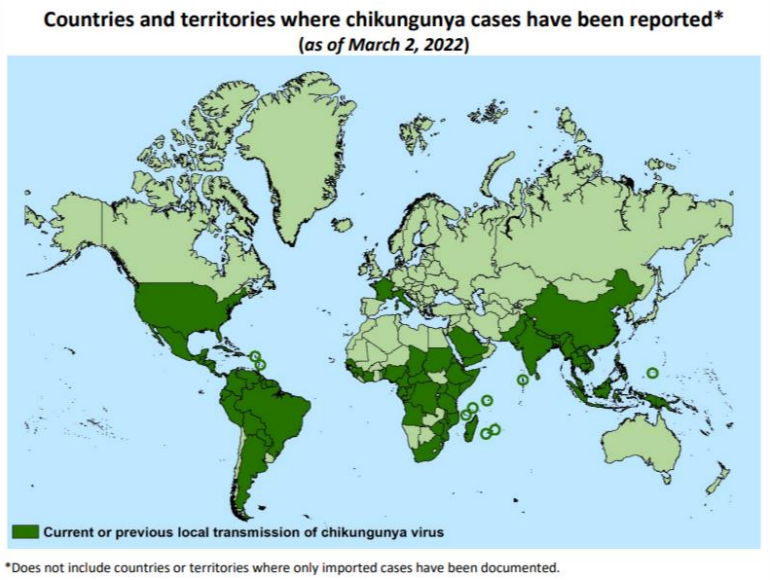
Vaccine for troops stationed in areas with risk of chikungunya

Outbreak Preparedness Non-Endemic Regions

Vaccine in areas in response to / at risk for a domestic outbreak

Endemic Region Use

Vaccine in endemic / LMIC markets, Targeted via **CEPI / Instituto Butantan Partnership**



1 VAMV005. Chikungunya virus vaccines. Global demand analysis. Feb 2020

VLA1553 Fits Perfectly Within our Existing Commercial Infrastructure

High-caliber team with significant experience in the vaccine space

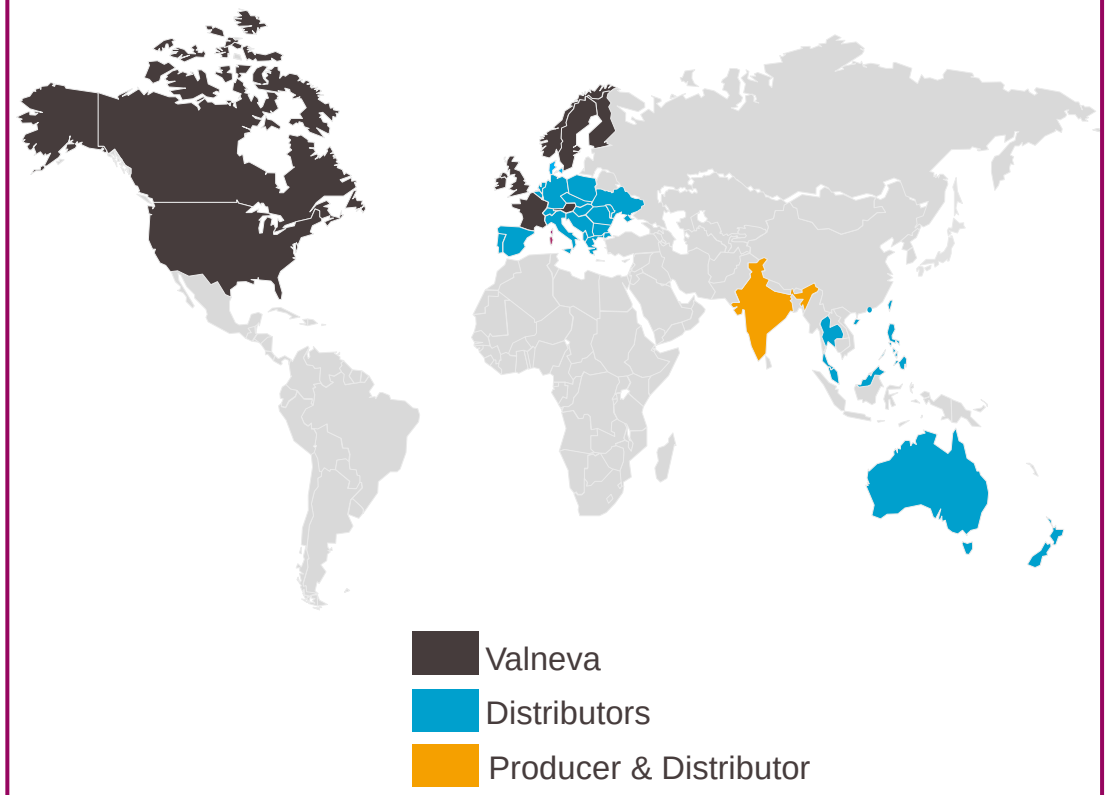
Highly experienced teams with deep expertise in vaccine commercialization

Commercial infrastructure present in most key travel markets; footprint extended through distribution partners

Integrated sales, marketing, medical and government affairs capabilities focused on unlocking brand potential

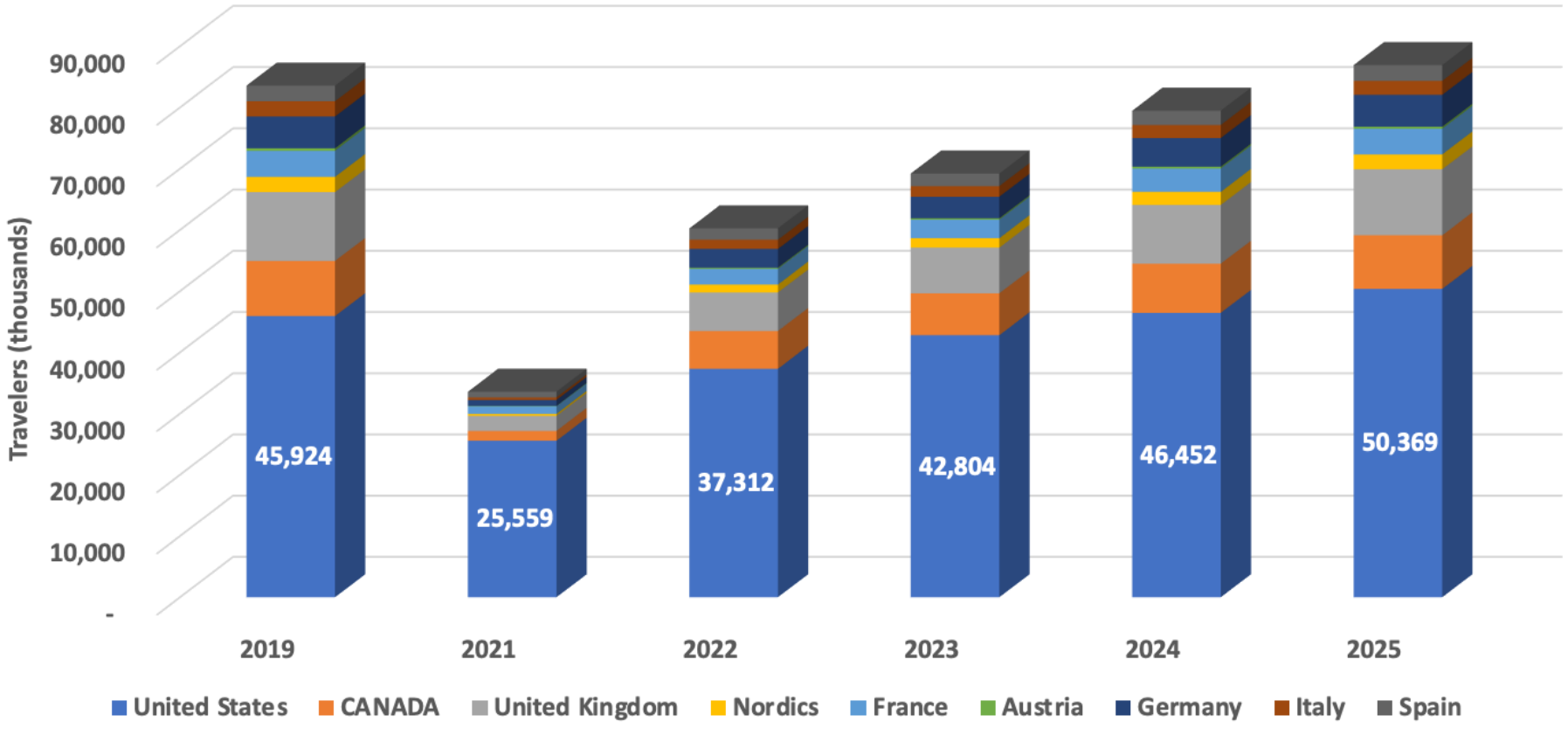
Leverage data driven insights and digital tools to enhance commercial capabilities

Commercial Footprint



Travel Recovery Underway

Outbound passengers from Valneva markets to CHIKV endemic markets

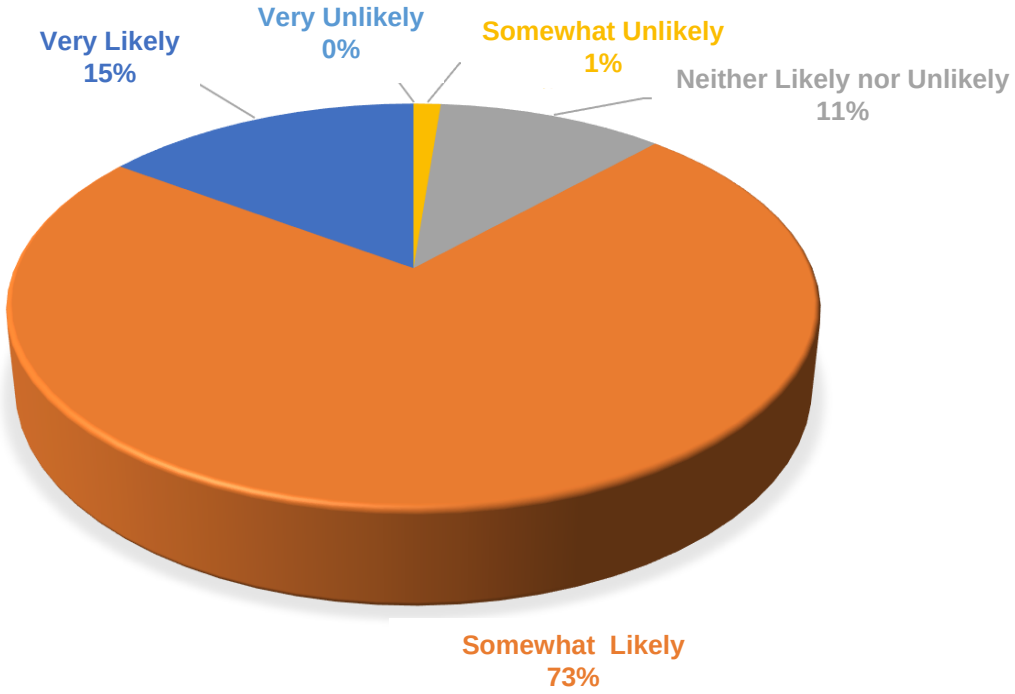


Source: 2022 IATA Passenger Forecast

Despite Low General Awareness, There is Considerable Interest in a CHIKV Vaccine Following Brief Introduction to the Disease

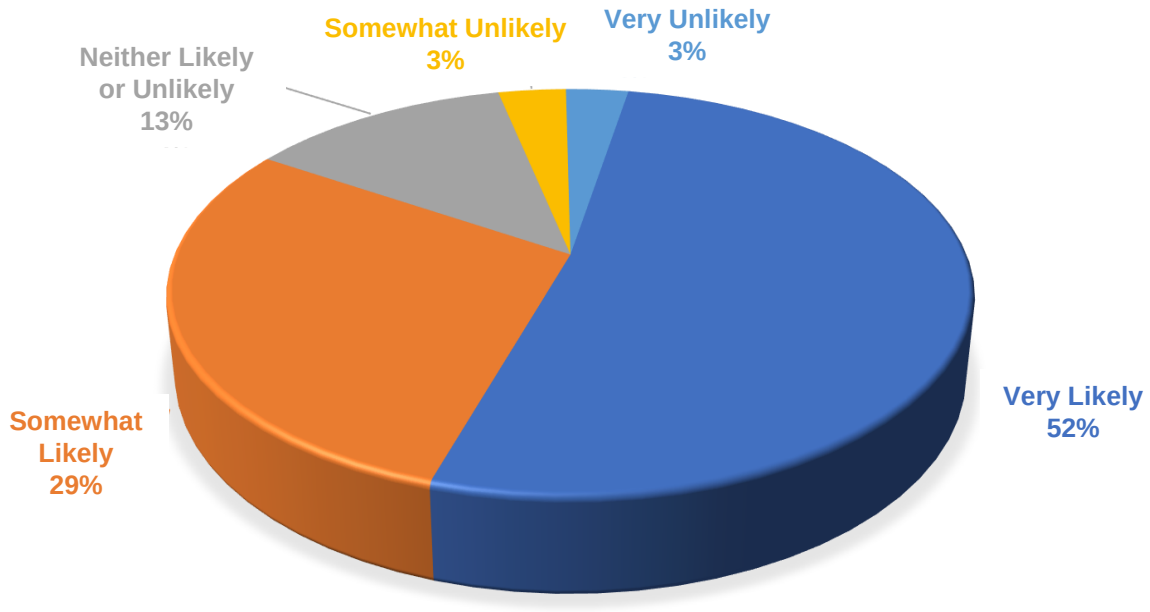
HCPs (n = 168)

Likelihood to recommend/prescribe a CHIKV vaccine if recommended by ACIP



Travelers (n = 2002)

If a doctor or HCP recommended the CHIKV vaccine for you, how likely would you be to get vaccinated



Source: Data on File. Global HCP Quantitative Research; Global Traveler Quantitative Research – US Respondents

Market Access Environment in the U.S. is Improving

Inflation Reduction Act ensures coverage for all ACIP-recommended vaccines without cost sharing

- **49 million Americans enrolled in Medicare Part D**
  - 10,000 people turn 65 every day in the U.S. 65+ population expected to exceed 70 million by 2030

- **CMS Guidance to Part D plans is clear, all ACIP-recommended vaccines must be covered:**

  ***CMS interprets "adult vaccine" and "vaccine … for use by adult populations**," solely for the purposes of section 1860D-2(b)(8) of the Act, to refer to those vaccines licensed by the FDA and recommended by ACIP for use in "adults," as described by the CDC/ACIP in the Adult Immunization Schedule or other applicable ACIP recommendations. **We also interpret the term "recommended" to mean all categories of ACIP recommendations,** including those that are specified as based on shared clinical decision-making.*

  We note that the ACIP Vaccine Recommendations and Guidelines also provide recommendations for use in limited populations and circumstances for certain other vaccines that are not on the CDC/ACIP Adult Immunization Schedule for routine immunization. We interpret the requirements of section 1860D-2(b)(8) of the Act also to apply to vaccines provided in such limited populations and circumstances, when used for adults in accordance with ACIP recommendations.

  *"Generally, Part D vaccines that have ACIP-recommended uses in the adult population and are being used for an adult must be provided with no enrollee cost sharing. **There is no enrollee cost sharing on the ingredient cost of the vaccine submitted on the prescription drug event (PDE) record, or any associated sales tax, dispensing fee, or vaccine administration fee, regardless of tier placement or benefit phase."***

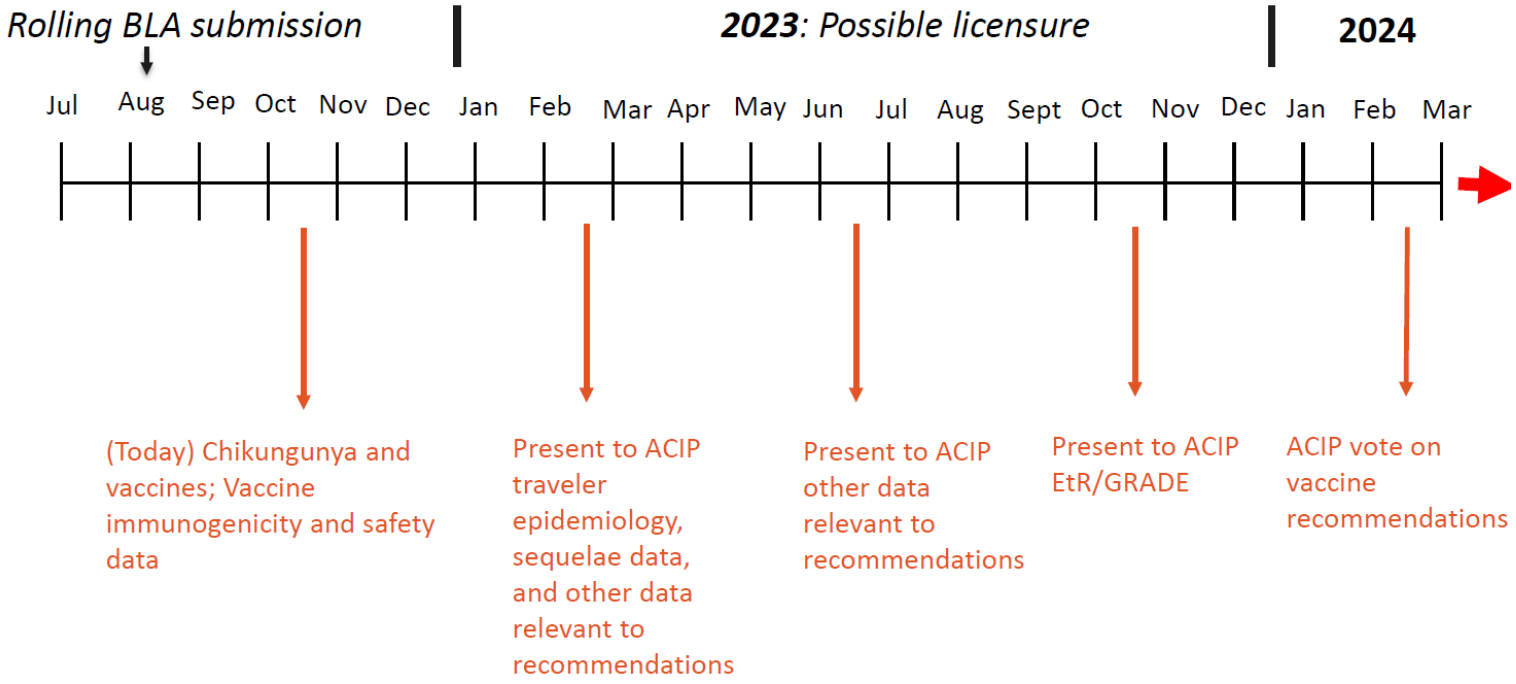
Source: CMS Guidance Memo, Sept. 26, 2022

ACIP Recommendation Process is Well-defined and in Process for VLA1553

U.S.: Vaccine policy is governed by CDC's Advisory Committee on Immunization Practices (ACIP)

- May 2022: Chikungunya Work Group constituted
- October 2022: Work Group and Valneva presented information about CHIKV and VLA1553 to ACIP
- February 2024: ACIP vote tentatively scheduled for Feb 2024 meeting

Work Group timeline (tentative)



VLA1553 has the Potential to Address a Significant Unmet Medical Need

- **Chikungunya (CHIKV) is a global public health threat with no effective treatments or prevention options**
- **CHIKV has both an acute and chronic phase – resulting in significant morbidity (e.g. chronic inflammatory rheumatism, etc.)**
- **Reported in over 100 countries, potentially impacting over 3.9 billion inhabitants**
- **The expanding habitat for the vectors can lead to further disease expansion (via imported cases, etc.)**
- **Global travel recovery under way, with outbound travel to CHIKV endemic markets back to 2019 levels by 2025**
- **VLA1553 fits perfectly within Valneva's infrastructure**

Sources: CDC, IATA, WHO

Valneva's & Pfizer's Lyme program

Thomas Lingelbach

Multivalent Recombinant Protein Vaccine Candidate for Lyme Disease

VLA15 - Only Lyme Disease Program in Advanced Clinical Development Today

1. **Phase 3 study initated[1] following positive results for three Phase 2 clinical trials[2,3,4], including first pediatric data[5]**
2. **Exclusive, worldwide partnership with Pfizer; terms updated in June 2022 in conjunction with Pfizer's €90.5 ($95) million equity investment in Valneva[6]**
3. **Investigational multivalent vaccine (six serotypes) to help protect against Lyme disease in the United States and Europe**
4. **Follows established mechanism of action for a Lyme disease vaccine candidate**
5. **Fast Track Designation granted by U.S. FDA in July 2017**

1 Pfizer and Valneva Initiate Phase 3 Study of Lyme Disease Vaccine Candidate VLA15; **2** Valneva announces positive initial results for Phase 2 study of Lyme Disease vaccine candidate**; 3** Valneva announces positive initial results for second Phase 2 study of Lyme Disease vaccine candidate VLA15. **4** Valneva and Pfizer Report Further Positive Phase 2 Data for Lyme Disease Vaccine Candidate **; 5** Valneva and Pfizer Report Positive Phase 2 Pediatric Data for Lyme Disease Vaccine Candidate/; **6** Valneva and Pfizer Enter into an Equity Subscription Agreement and Update Terms of Collaboration Agreement for Lyme Disease Vaccine Candidate VLA15;

Valneva's and Pfizer's Collaboration to Co-Develop and Commercialize Lyme Disease Vaccine, VLA15

Key features

Established	April 2020
Updated	June 2022; Equity Investment of $95 Million by Pfizer; Phase 3 cost split 40/60% (Valneva/Pfizer)*
Rationale	Maximize Lyme disease opportunity by leveraging Pfizer's outstanding development and commercial expertise
Scope	Pfizer leading late-stage development and will have sole control over global commercialization
Key Financial Terms	Valneva eligible to receive up to $408 million ($165 million received) • $130 million upfront payment (received) • $35 million in development milestone payments (received) • $143 million in early commercialization milestones • $100 million in cumulative sales milestones Tiered sales royalties ranging 14-22%
Co-development costs	Valneva responsible for 40%; Pfizer 60%
Status	Pivotal Phase 3 study currently enrolling adult and pediatric participants

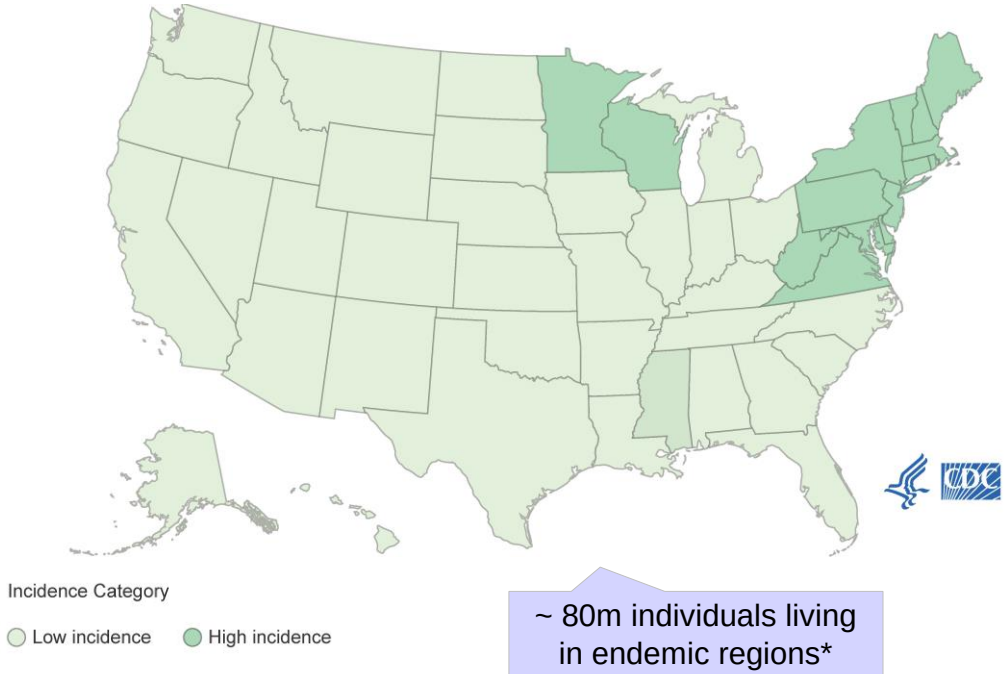
* As of 1st May 2022

Lyme Disease is a Major Health Issue

Severe Tick-transmitted Infection, Increasingly Common in the U.S. and Europe

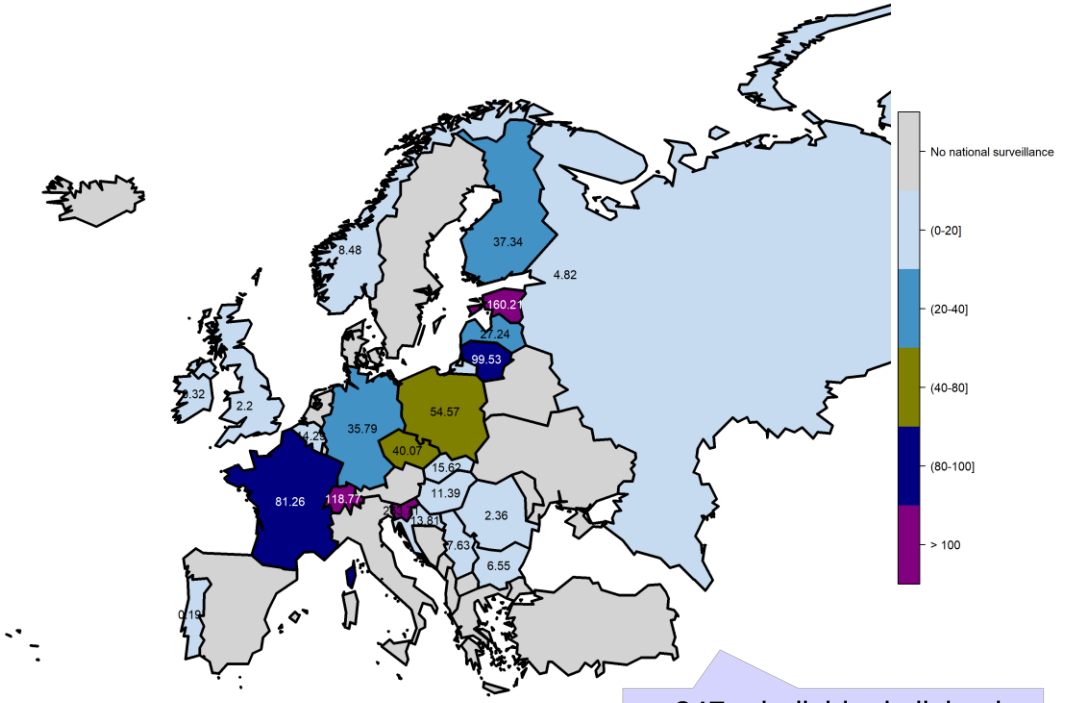
Epidemiology – Seasonal (peaking in ~ July)

National Surveillance by Incidence Category
(~475,000 annual cases)



~ 80m individuals living in endemic regions*

Incidence for three most recent available years
(cases/100,000 persons) (> 130,000 annual cases)



~ 247m individuals living in endemic regions*

US: CDC https://www.cdc.gov/lyme/stats/maps.html, EU: Pfizer internal analysis of national surveillance system data

* Endemic regions are defined by an incidence of >10/100.000 population

Lyme Borreliosis Can Progress to Serious Life-Altering Symptoms

Clinical Manifestations of Lyme Borreliosis

Early localized disease

- 3-30 days after tick bite
- Erythema migrans (70-90% of patients)
- Non-specific flu-like symptoms including fatigue and musculoskeletal pain

Disseminated disease

- Days, weeks, months after initial infection
- Neuroborreliosis including meningitis, facial palsy, radiculoneuropathy (~10% of patients)
- Lyme carditis (1-2% of patients)
- Lyme arthritis (~10-20% of patients)
- Acrodermatitis chronica atrophicans (Europe)
- *Borrelia lymphocytoma* (Europe)

Persistent symptoms

- Inadequate or poor response to treatment
- Post-treatment Lyme disease (~10-20% of all patients)
- Post-infectious Lyme arthritis (~10-20% of arthritis patients)
- Autoimmune neurologic disease

CDC https://www.cdc.gov/lyme/signs_symptoms/index.html; Halperin et al. Lyme Disease and Other Infections Transmitted by Ixodes scapularis. 2018; Steere JCI 2020; Lantos et al. CID 2020

Potential Vaccination Against Lyme Disease Addresses an Unmet Medical Need

Prevention by vaccine would be a significant improvement over current preventive and treatment strategies

- Lyme borreliosis is emerging in new areas as Ixodes ticks are expanding their habitat
- The factors that put populations at risk continue to increase
- Lyme borreliosis can be treated successfully especially if identified early, but:

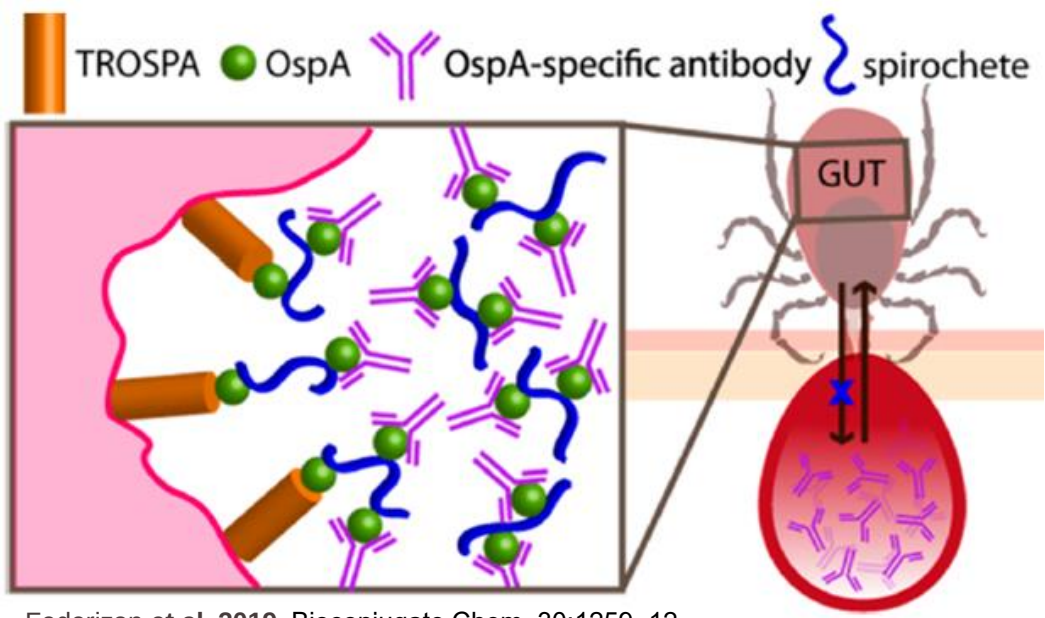
Physical prevention strategies* have limited effectiveness or poor compliance	Antibiotic prophylaxis after tick bite effective but bite often unnoticed	Early disease may be missed (by physician or patient)	Diagnosis at all stages can be challenging	Potential for severe manifestations and sequelae

*E.g., insect repellant, protective clothing, self-examination for ticks/tick bites, etc.

Established Mechanism of Action: Target Borrelia OspA

Transmission blocking – protection mediated by serum antibodies ingested by the tick

Anti-OspA antibodies against different Borrelia serotypes anticipated to mediate effector function in the tick through a common mechanism of action



Federizon **et al. 2019,** Bioconjugate Chem. 30:1259−12

OspA adhesin

- Binds to Tick Receptor for OspA (TROSPA)
- Highly expressed on bacterial surface while in the tick, turned off with migration to host

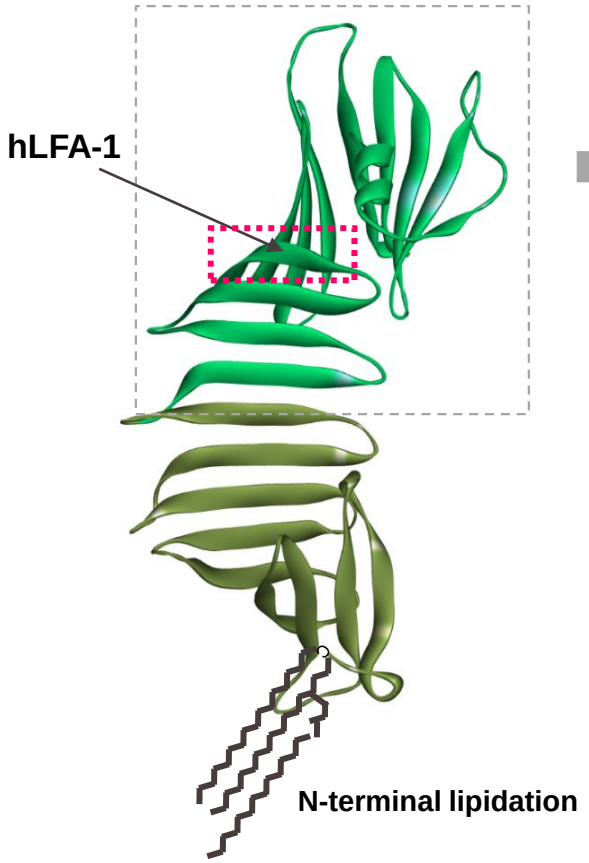
› Antibody to OspA neutralizes bacteria in the tick, blocking transmission to host

› Antibody mediated mechanism not well understood

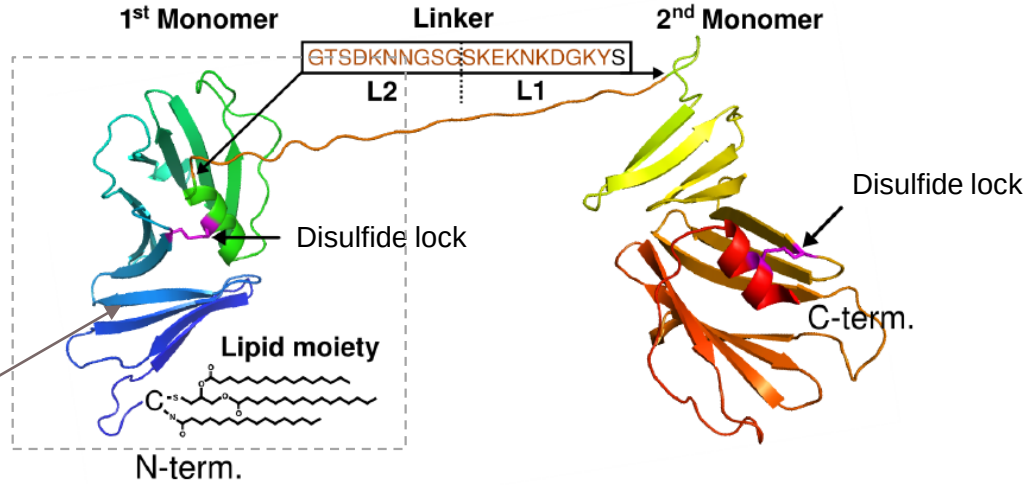
VLA15: A Multivalent Recombinant Protein Vaccine Candidate

LYMErix™/Immulyme® full-length Serotype 1

C-terminal region contains protective epitopes[1]



VLA15 fusion protein concept applicable for all serotypes[2]



hLFA-1 replacement (ST1)

Native ST1: Y V L E G T

VLA15 ST2: F T L E G K

- OspA C-terminal monomers are stabilized through introduction of disulfide bonds[2]
- Lipidation and Alum adjuvant increase immunogenicity
- Postulate that OspA vaccines might induce antibiotic-refractory Lyme arthritis due to molecular mimicry to human LFA-1* epitope was disproven for LYMErix[3,4]

1, Golde et al. 1997 Inf. Imm. 65:882-9. **2**, Comstedt et al. 2014, PLoS One 9:e113294; Comstedt et al. 2015, Vaccine 33:5982-8. **3,** Lathrop et al. 2002, Vaccine 20:1603-8.
4, Steere et al. 2011, CID 52 (Suppl 3) S259, ***** Leucocyte Function-associated Antigen-1

Prior Ospa Vaccines Showed Efficacy in Humans

History of prior Lyme vaccines (serotype 1 only)

LYMErix Phase 3 efficacy study

Dosing	Vaccine Efficacy (95% CI)
Y1 (0, 1M)	49% (15-69)
Y2 (0, 1, 12M)	76% (58-86)

Steere et al. 1998 N Engl J Med. 339:209-15

Product was removed from market after a few years for multiple reasons[1]

Immulyme® (Sanofi) Phase 3 efficacy study

Dosing	Vaccine Efficacy (95% CI)
Y1 (0, 1M)	68% (36-85)
Y2 (0, 1, 12M)	92% (69-97)

Sigal et al. 1998, N Engl J Med. 339:216-22

Product was never brought to market

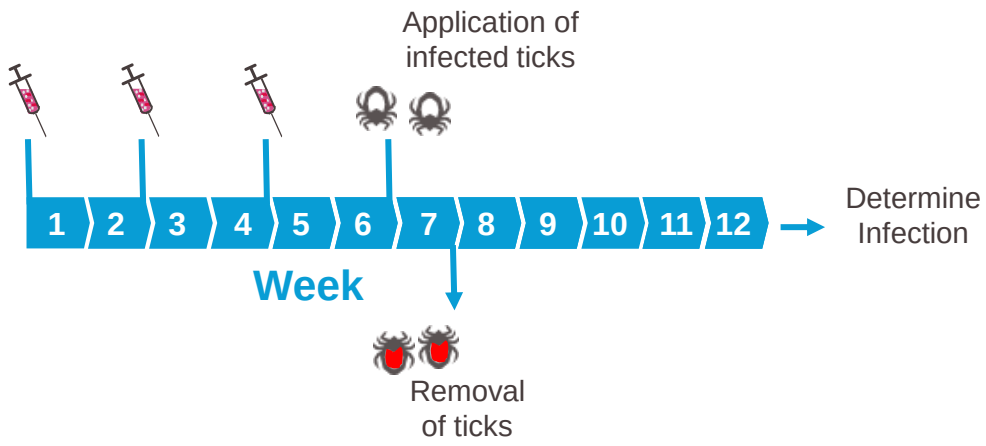
VLA15 Protects Against Infection in Tick Challenge Mouse Model

Proof-of-concept

Active Immunization

VLA15 was as efficacious as native full-length OspA

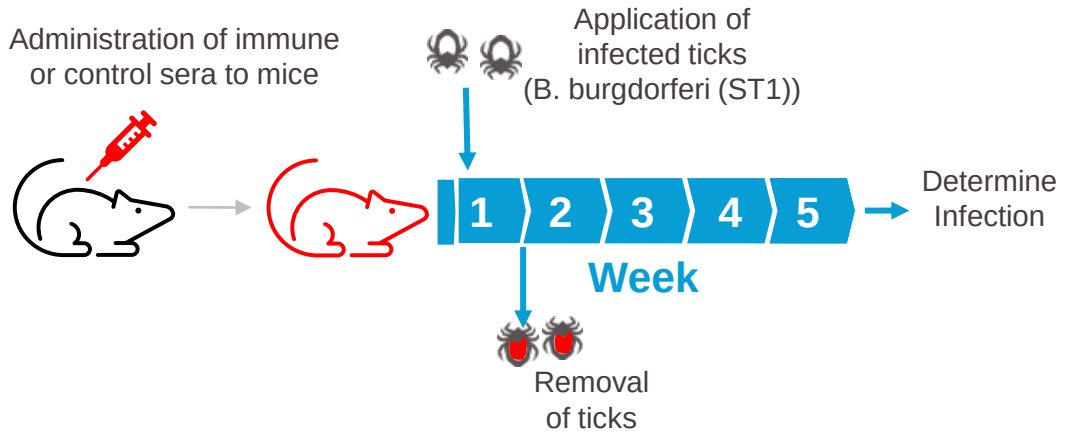
Immunization		Infection (infected/total)		
Immunogen	Dose	*B. burgdorferi* Pra1 (ST1)	*B. afzelii* IS1 (ST2)	*B. bavariensis* Marx1 (ST4)
Lip-OspA	1 µg	2/17**	0/17***	0/11***
VLA15	3 µg	0/18***	0/16***	0/11***
Placebo	-	9/13	13/13	12/15



Passive Transfer

Low dilutions of VLA15 human sera were protective

Human serum for passive transfer	GMT post transfer (U/mL)	Infection infected/total	P value
Neat VLA15-202 serum pool	1196	0/9	0.0090
1:2 diluted VLA15 pool	559	0/10	0.0031
1:4 diluted VLA15 pool	256	1/8	0.0498
1:8 diluted VLA15 pool	131	1/9	0.0498
Non-immune serum	negative	6/9	n/a



VLA 15 is currently in Phase 3 clinical development

Overview Development Plan

Valneva			Co-development Valneva/ Pfizer					
2017	2018	2019	2020	2021	2022	2023	2024	2025

Phase 1 First-in-Human study
Population: 18-39 yrs
12 µg, 48 µg, 90 µg +/- Alum
Month 0-1-2, Booster M 12-15

✓ VLA15 generally safe and immunogenic
Adjuvanted groups more immunogenic than non-adjuvanted, good boosterability

VLA15-201, 18-65 yrs
(90 µg), 135 µg, 180 µg + Alum
Schedule: Month 0-1-2

✓ **VLA15-201/202**: Higher doses of VLA15 generally safe and immunogenic → dose decision VLA15 180 µg

VLA15-202: A M18 booster dose induced strong anamnestic response

VLA15-202, 18-65 yrs
135 µg, 180 µg + Alum
Schedule: Month 0-2-6, Booster M18

ongoing

First study that includes pediatric subjects, comparison of M0-2-6 vs M0-6 schedule → schedule decision M0-2-6

VLA15-221, 5-65 yrs; VLA15 180 µg w/ Alum
Schedule: Month 0-2-6 vs Month 0-6
M18 booster with 3 yrs FU

ongoing

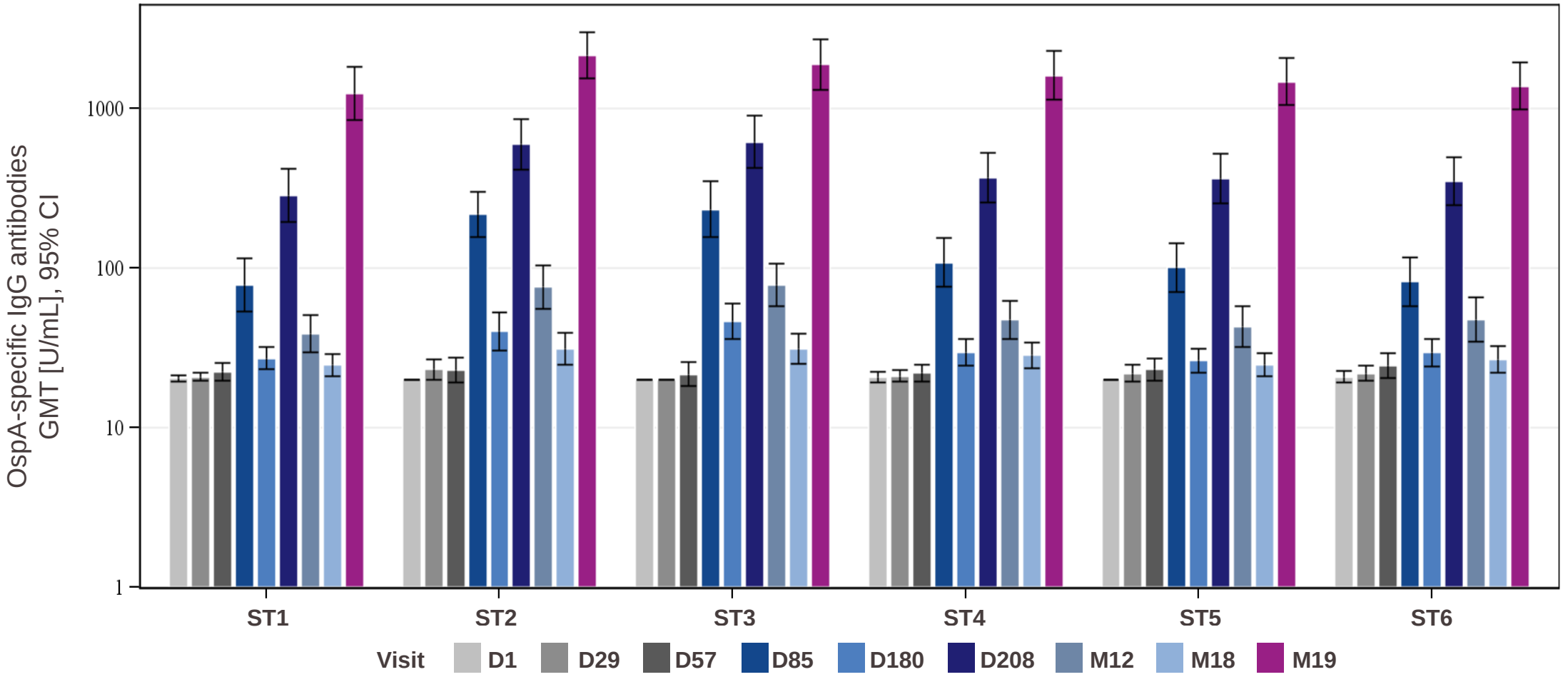
VALOR
Vaccine Against Lyme for Outdoor Recreationists

Phase 3 development ≥ 5 years
VLA15 180 µg w/ Alum
Schedule: Month 0-2-6, Booster M18

ongoing

VLA15 Showed Strong Immunogenicity Including Anamnestic Response

VLA15-202 data (adults) including post booster results

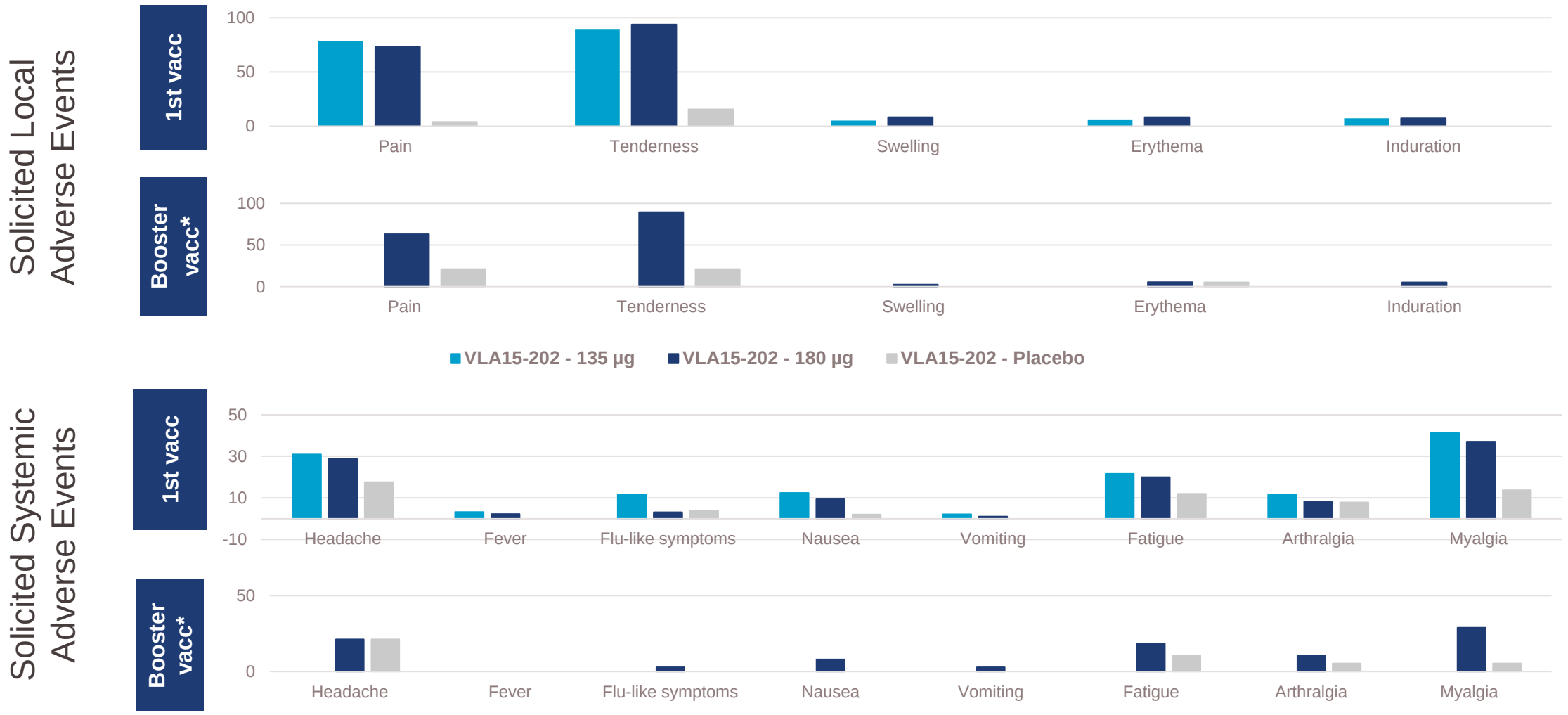


ELISA results <40 U/mL are replaced by 20 U/mL.

Booster PP Population

Safety Profile: VLA15 Generally Well Tolerated, Consistent with Lipidated Vaccines

VLA15-202: AE rates after booster compared to after primary vaccination



***A booster dose was given to trial participants receiving VLA15 180 µg only**

VLA15 Demonstrated Strong Immunogenicity Across 1,030 Adult and Pediatric Participants

VLA15-221: First positive pediatric data (April 2022[1])

- Strong immunogenicity profile in adult [2] (ages 18-65) and pediatric participants (ages 5-17)
- More immunogenic in pediatric participants than in adults, with both two-dose and three-dose vaccination schedules; three-dose schedule selected for all ages in Phase 3

VLA15-202: First positive booster data (September 2021)[3]

- High antibody responses confirmed across all serotypes and dose groups after primary vaccination series (primary endpoint)[4]
- 12-month booster dose elicited strong anamnestic response

VLA15-201: First positive immunogenicity data (July 2020)[5]

- Immunogenic across all serotypes and dose groups; higher doses elicited higher antibody responses
- Encouraging immunogenicity profile confirmed, including in older adults (ages 50-65)

1 Valneva and Pfizer Report Positive Phase 2 Pediatric Data for Lyme Disease Vaccine Candidate; **2** Valneva and Pfizer Report Further Positive Phase 2 Data for Lyme Disease Vaccine Candidate; **3** Valneva and Pfizer Report Further Positive Phase 2 Results, Including Booster Response, for Lyme Disease Vaccine Candidate, 4 Valneva Announces Positive Initial Results for Second Phase 2 Study of Lyme Disease Vaccine Candidate VLA15 **5** Valneva Announces Positive Initial Results for Phase 2 Study of Lyme Disease Vaccine Candidate

VLA15-221: Six-month Antibody Persistence Results in Children and Adults

Data further validate ongoing Phase 3 study design

Antibody levels remained above baseline six months after completion of a three-dose (Month 0-2-6) or a two-dose (Month 0-6) vaccination schedule

- First antibody persistence data reported in pediatric populations for this vaccine candidate

Higher antibody levels observed for the three-dose vaccination schedule versus the two-dose vaccination schedule

- Further validates use of this schedule in the ongoing Phase 3 study

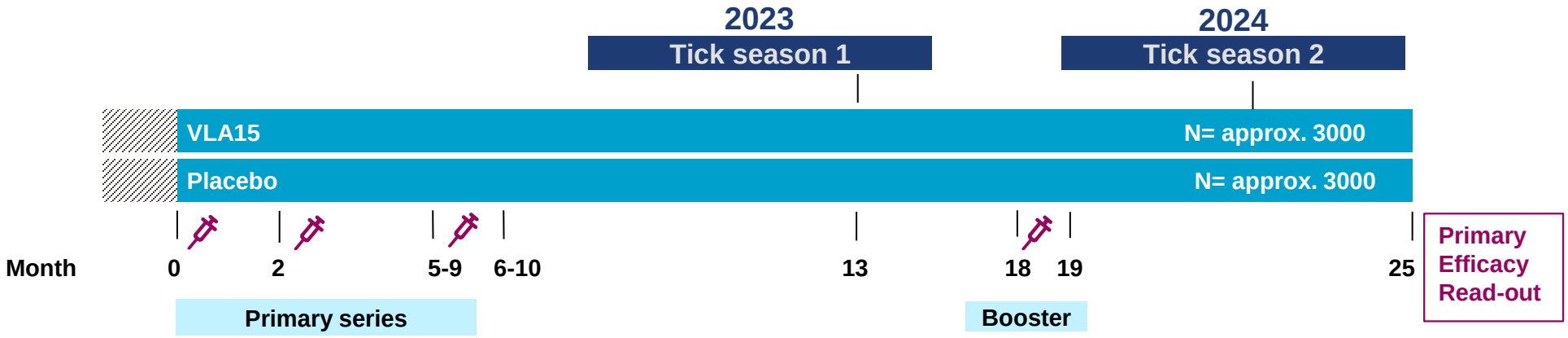
No safety concerns observed in this six-month observational follow up

- No vaccine-related serious adverse events (SAEs)

Phase 3 Efficacy Study Currently Enrolling

Randomized, Placebo-Controlled Phase 3 VALOR Study Design

- **Population**: 6,000 participants ≥5 years of age at high risk of Lyme disease (LD) (by residence and occupational/recreational activities) conducted in US and Europe (randomization approx. 2:1 US/EU)
- **Primary endpoint:** Rate of confirmed[1] LD cases after 2nd Lyme season (i.e., after completion of full vaccination series 3+1)
- **Secondary endpoints** include rate of confirmed[1] LD cases after 1st Lyme season (i.e., after completion of primary vaccination series) amongst other secondary endpoints as defined in Phase 3 protocol



Expect enrollment completion in 2Q 2023. Pending successful completion of the Phase 3 study, Pfizer could potentially submit a Biologics License Application (BLA) to the U.S. Food and Drug Administration (FDA) and Marketing Authorization Application (MAA) to the European Medicines Agency (EMA) in 2025.

1 Cases will be evaluated and confirmed by an Endpoint Adjudication Committee

Building Future R&D Pipeline

Thomas Lingelbach

Valneva Pre-Clinical Pipeline and Selected Indications

Attractive Indications with High Unmet Medical Need

	Program	Approach	Discovery	Pre-Clinical	Phase 1	Upcoming Milestones	Partnership
Pre-Clinical Projects	**VLA1554:** hMPV	Subunit + Adjuvant				Pre-clinical PoC	In-house
	VLA2112: EBV	Subunit + Adjuvant				Evaluation of vaccine candidate	Evaluation & Option, In-house
	VLA1801: Parvovirus	VLP + Adjuvant				Evaluation of vaccine candidate	Evaluation & Option
	VLA2111: Campylobacter	Inactivated + Adjuvant				Evaluation of technology	Evaluation & Option

Select Pre-Clinical Assets

Anders Lilja

Human Metapneumovirus (hMPV)

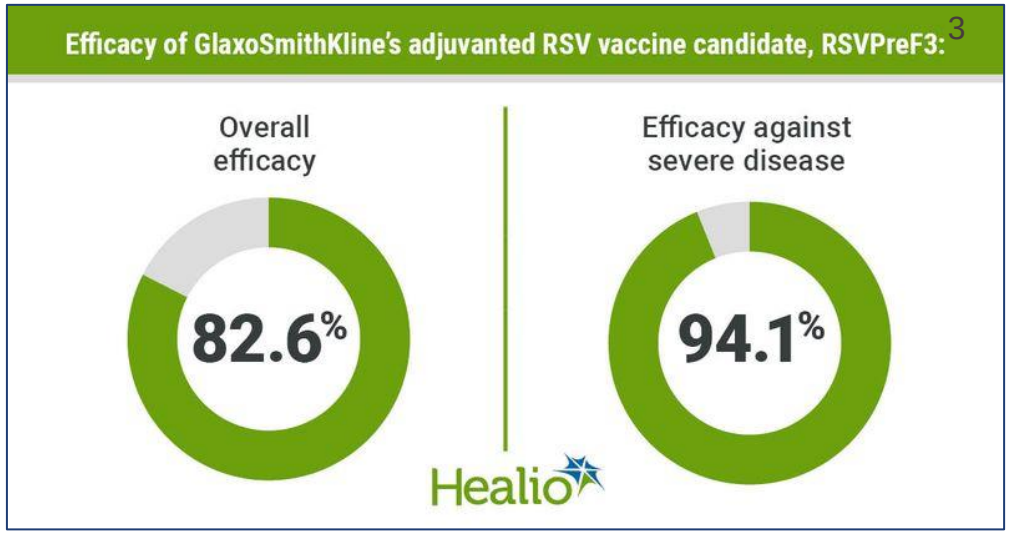
After 50 Years of Failures, There Will (Subject to Approvals) be RSV Vaccines

Pfizer Announces Positive Top-Line Data of Phase 3 Global Maternal Immunization Trial for its Bivalent Respiratory Syncytial Virus (RSV) Vaccine Candidate[1]

Pfizer

Pfizer Announces Positive Top-Line Data of Phase 3 Global Maternal Immunization Trial for its Bivalent Respiratory Syncytial Virus (RSV) Vaccine Candidate[2]

Pfizer

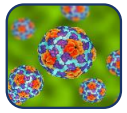


- **What is the next greatest medical need for respiratory viruses?**
- **What lessons learned from closely related RSV can be applied?**

1 https://www.pfizer.com/news/press-release/press-release-detail/pfizer-announces-positive-top-line-data-phase-3-trial-older; 2 https://www.pfizer.com/news/press-release/press-release-detail/pfizer-announces-positive-top-line-data-phase-3-global; 3 https://www.healio.com/news/infectious-disease/20221020/multiple-rsv-vaccines-in-latestage-development-show-promise-in-older-adults - derived from Ison MG, et al. Abstract LB745. Presented at: IDWeek; Oct. 19-23, 2022

Human Metapneumovirus (hMPV)

Human Metapneumovirus



Enveloped, ssRNA virus
Natural infection doesn't prevent re-infection
Structurally complex surface antigen (F protein)

Part of *Pneumoviridae* family alongside RSV
2 circulating subgroups, A & B. Identified in 2001.

Airborne & direct contact transmission

Epidemiology

2nd most common viral upper respiratory tract infection
- 6 – 12 million cases/year in US/EU
- Global distribution

Accounts for 5 - 10% of all viral respiratory tract infections[1,2]

Young children, immunocompromised, and elderly

3.4 – 6.6% mortality in hospitalized adults

Disease

Causes acute respiratory illness (ARI) with cough, sore throat, wheezing & difficulty in breathing

Annual, seasonal virus. Symptoms occur 3 – 6 days post-exposure

Can lead to bronchiolitis and pneumonia

No specific treatment

Prevented by frequent hand washing & cleaning infected surfaces

Vaccine development

Goal: Prevention of hMPV infection in elderly & at-risk adults

Candidate: Valneva-generated recombinant F protein i.m. route with adjuvant

MoA: Anti-F protein neutralizing antibodies and T cell response

Market Potential: $1 – 1.6 billion[3]

Moderna in phase 1b with combo hMPV/PIV3

1, Taylor et al., Journal of infection (2017); 2, Principi & Esposito, Journal of Clinical Virology (2016); 3 Company estimates (2019)

General information: Li et al, Lancet Glob Health (2019); CDC: https://www.cdc.gov/surveillance/nrevss/hmpv/clinical.html#prevention

Competitive Landscape – hMPV Vaccine Candidates

Currently in development

Company	Phase	Platform	Indications	hMPV antigen	Comments
Moderna	1	mRNA LNP	hMPV/PIV	Full-length F[1]	Phase 1 completed, data reported[1]
Icosavax	1	Subunit nanopart.	hMPV/RSV	Pre-fusion F	Phase 1 started October 2022[2]
Valneva	Preclin.	Subunit	hMPV	Pre-fusion F	
NIAID	Preclin.	Subunit nanopart.	hMPV	Pre-fusion F	

- Moderna reported an overall 6-fold boost of hMPV-neutralizing antibodies in previously exposed adults, 18-49 years of age, but the response was not dose dependent[1]
- In comparison, the NIAID[3] and Pfizer[4] RSV vaccines elicited 10- to 12-fold and 10- to 20-fold boosts, respectively, in previously exposed adults, 18-49/50 years of age
- Although different indications, this hints at room for an improved hMPV vaccine

1 August et al. 2022, OFID 9(7):ofac206. doi: 10.1093/ofid/ofac206; 2 https://investors.icosavax.com/news-releases/news-release-details/icosavax-initiates-phase-1-trial-ivx-a12-against-rsv-and-hmpv;
3 Ruckwardt et al. 2021, Lancet Respi Med 9(10):1111-1120; 4 Walsh et al. 2022, J Infect Dis 225:1357–66

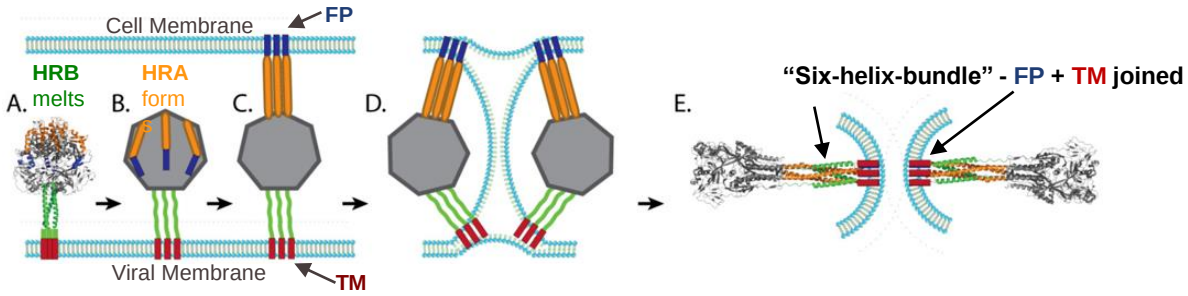
VLA1554: Valneva's Proprietary hMPV Vaccine

Selection of hMPV vaccine approach

Utilize experience from RSV vaccines for hMPV vaccines

- The breakthrough that ultimately enabled efficacious RSV vaccines was the discovery of the pre-fusion form of the F protein and the subsequent engineered, stabilized pre-fusion F antigen (Pfizer and GSK vaccines)

HRA - heptad repeat A
HRB - heptad repeat B
TM – transmembrane domain
FP – fusion peptide



Pre-fusion Intermediate → collapses to Post-fusion

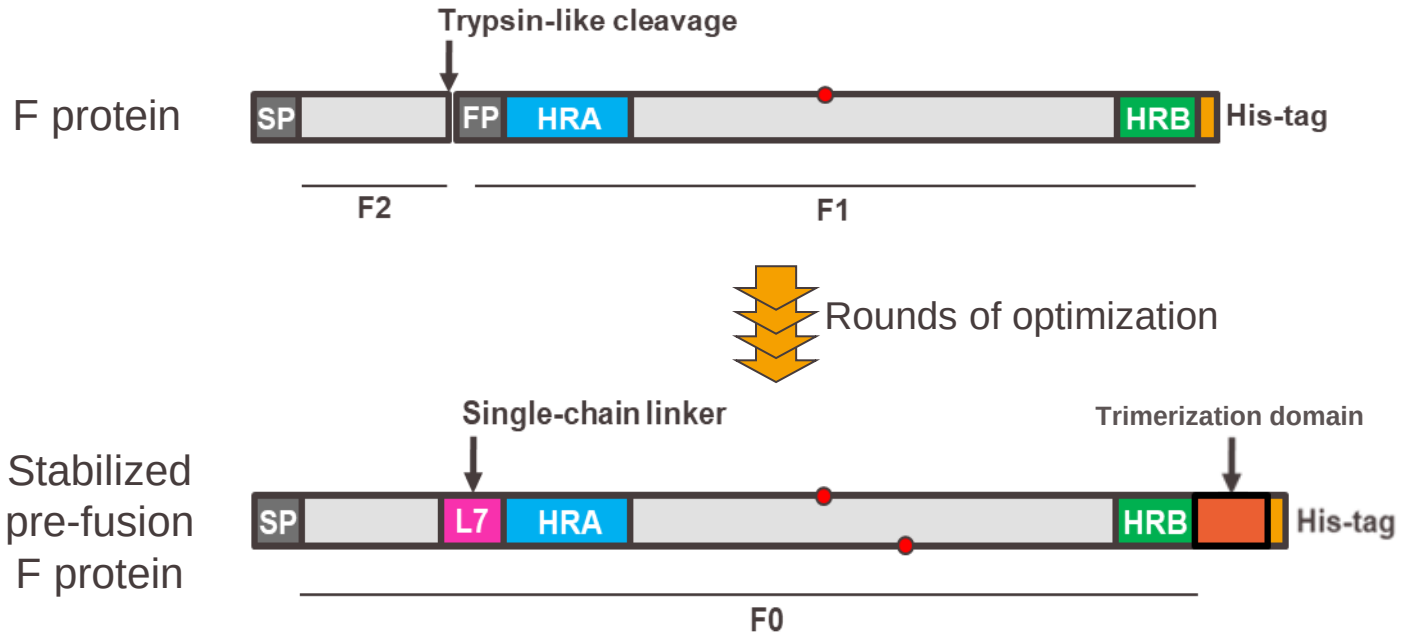
Design of hMPV vaccine

- Antigen selection: pre-fusion F protein, immunodominant and highly conserved
- Desired immune response: high level of neutralizing antibodies, avoid Th2-biased response
- Desired vaccine coverage: protection against subgroup A and B strains
- Vaccine composition: adjuvanted subunit protein
- Potential to combine with RSV vaccine

Valneva's Recombinant Pre-Fusion F Protein Antigen

Structure-based vaccine antigen design

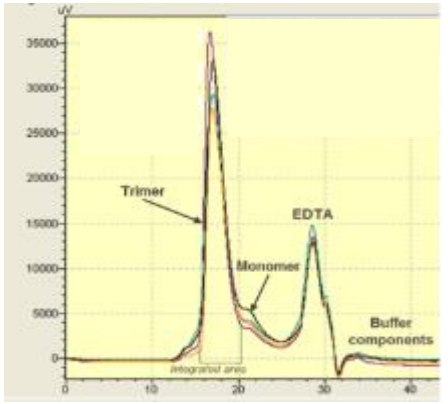
- Successfully generated stable pre-fusion F protein after multiple rounds of optimization and characterization
- Modifications based on bioinformatic modelling to avoid interference with known neutralizing epitopes



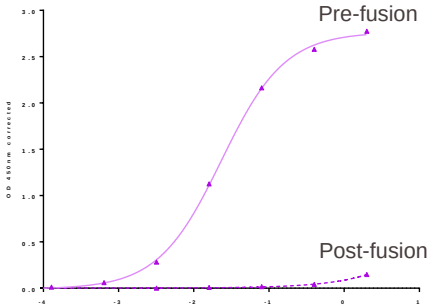
Antigen characterization

Purity and yield
(SDS-PAGE + UV quantification)

Trimers/monomers/aggregates
(SE-HPLC)



Conformation
(Pre-/post-fusion specific ELISA)



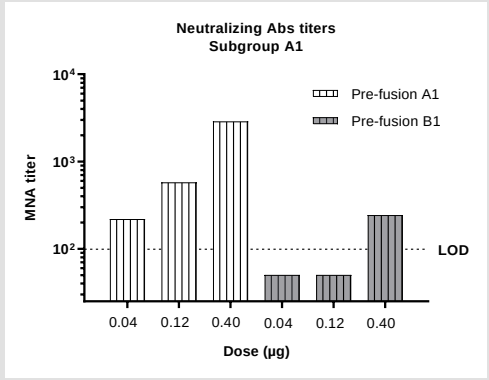
VLA1554 Protects Against hMPV A1/2 and B1 in hMPV Mouse Model

Functional immune responses observed at low doses

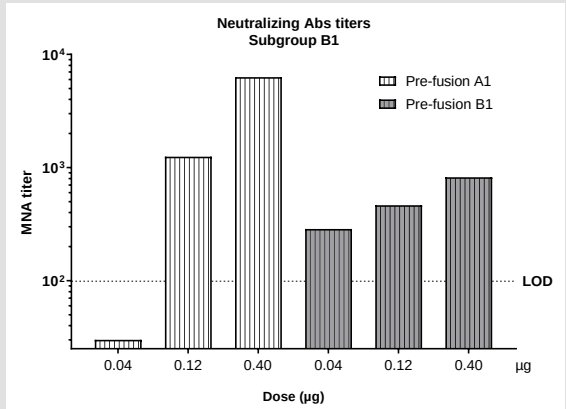
Mice were immunized with different doses of adjuvanted, pre-fusion A1 or B1 F protein (i.m. Days 0, 14, 28) and challenged with subgroup A2 hMPV virus (Day 42)

- Neutralizing titers were determined against A1 and B1 hMPV virus by microneutralization assay (MNA)
- Viral load in the lung following challenge (A2) analyzed by focus-forming assay (FFA)

Neutralization of hMPV A1

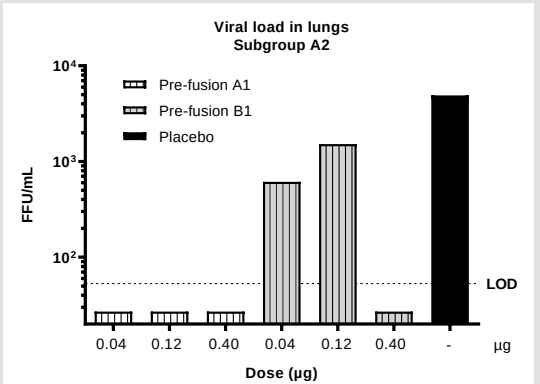


Neutralization of hMPV B1*



*separate mouse study from the two other panels

Protection against hMPV A2 challenge



- Functional immune responses observed against both hMPV A and B subgroups
- No infectious virus detected in lungs after immunization with pre-fusion A1 F protein at all doses tested
- Immunization with pre-fusion A1 F protein generated superior immune responses against both subgroup A and B hMPV as compared to pre-fusion B1 F protein; Superior protection following viral challenge with hMPV subgroup A2

VLA1554: hMPV Vaccine

Summary

- Valneva's proprietary hMPV vaccine candidate is based on an adjuvanted, subunit, stabilized pre-fusion F protein
- The stabilized pre-fusion F candidate is proprietary to Valneva
- The vaccine candidate is produced in CHO cells, an initial classical purification process has been established with suitable production yield
- Immunization with pre-fusion A1 F protein generated superior neutralizing antibody response against hMPV subgroups A1 and B1 as compared to pre-fusion B1 F protein
- Low doses of the vaccine candidate generated hMPV-neutralizing responses that protected mice from challenge
- Adjuvant evaluation currently in progress

Epstein-Barr Virus (EBV)

Prevention of Epstein-Barr Virus Infection is an Unmet Medical Need

Infectious mononucleosis, multiple sclerosis, and cancer

Epstein-Barr Virus (EBV)

- Gammaherpesvirus, human herpesvirus 4
- Transmitted through saliva and other bodily fluids
- >95% of population infected by age 25
- Stays with the host for life

Infectious mononucleosis

- Estimated ~45 per 100,000 per year (90% caused by EBV)
- Symptomatic disease primarily in adolescents and young adults: fever, sore throat, fatigue, malaise, swollen lymph nodes & spleen
- Symptoms last 2-4 weeks, rarely fatigue lasts for months
- Acute complications in approx. 1%

Multiple sclerosis

- Global reported incidence 2.1 per 100,000 per year[1]
- Risk of MS increases 32-fold after EBV infection[2]

Cancer

- Implicated in Burkitt's lymphoma, Hodgkin's lymphoma, post-transplant lymphoproliferative disease (PTLD), nasopharyngeal carcinoma, gastric carcinoma, and T & NK cell lymphomas

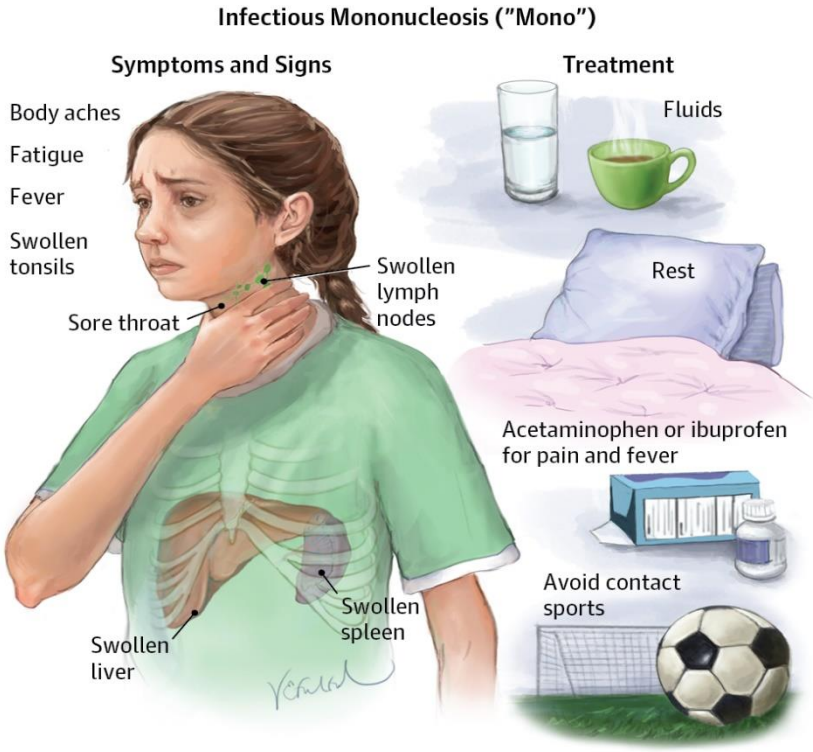
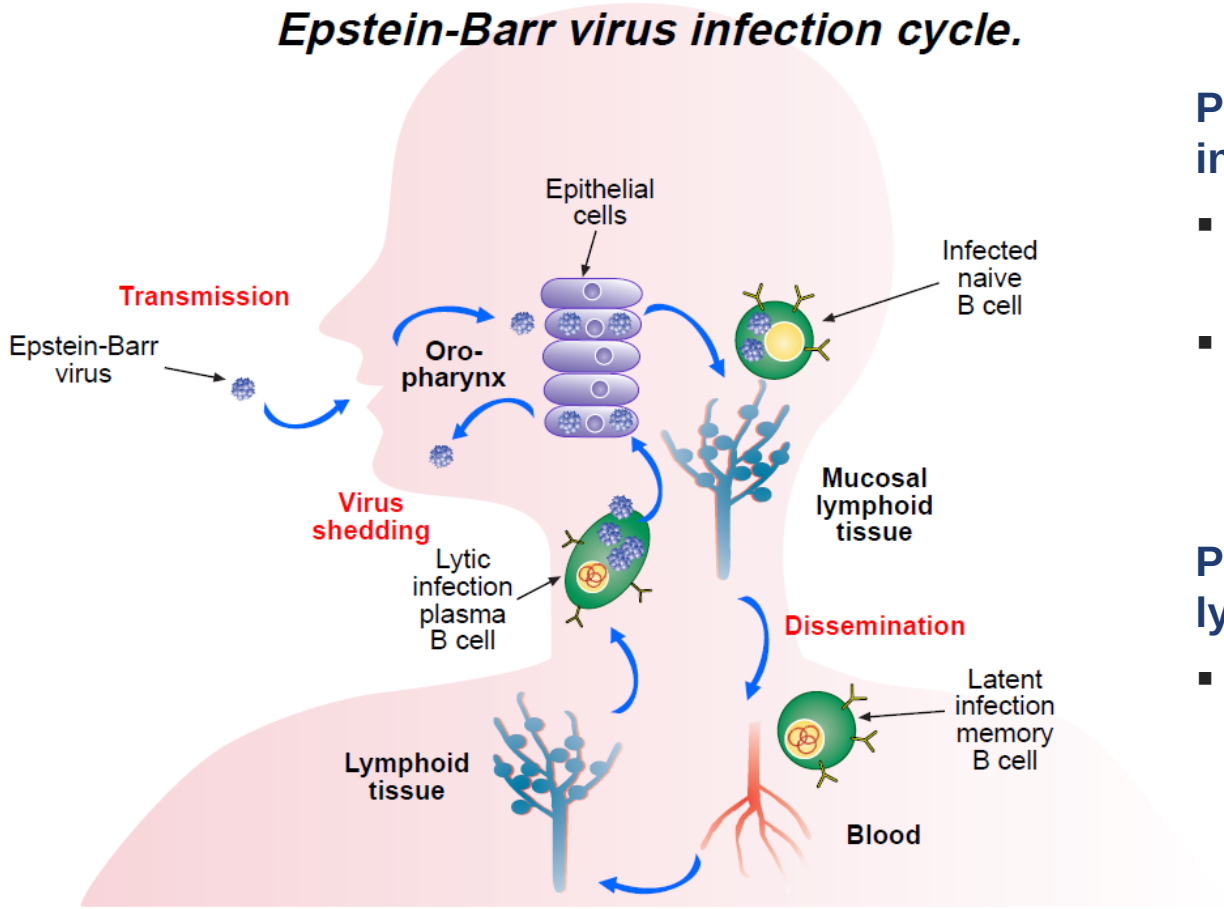


Figure from Thompson 2015. *JAMA*. 2015

1 Walton et al 2020 *Mult. Scler.,* 2 Bjornevik et al 2022 *Science*

How Do You Prevent Clinically Relevant Epstein-Barr Virus Infection?

Two points of intervention: epithelial cells and B cells



www.immunopaedia.org.za/immunology/archive/cytokine-storm/epstein-barr-virus-ebv/

Prevent infection and carcinomas by blocking infection of epithelial cells

- Viral glycoprotein gH/gL binds integrins to enable infection of epithelial cells[1]
- gH/gL-specific antibodies block EBV infection of epithelial cells (and B cells)[2,3]

Prevent infectious mononucleosis and B cell lymphomas by blocking infection of B cells

- Viral glycoprotein gp350 enables infection of B cells by binding to CD21[4]

1 Chesnokova et al 2009 *Proc. Natl. Acad. Sci. USA;* 2 Bu et al 2019 *Immunity;* 3 Chen et al 2022 *Immunity;* 4 Nemerow et al 1987 *J. Virol.*

Prior Vaccine Candidate Reduced Incidence Of Mononucleosis But Not Infection

Informs design of second-generation vaccine candidates

- GSK developed a gp350 subunit protein vaccine adjuvanted with AS04 to Phase 2
- Vaccine recipients had a statistically significant 78% lower incidence of infectious mononucleosis than placebo recipients, although the number of cases was low[1]

Case, presentation category	ATP population		ITT population	
	Given placebo (n = 90)	Given gp350/AS04 vaccine (n = 86)	Given placebo (n = 91)	Given gp350/AS04 vaccine (n = 90)
Infectious mononucleosis	8	2	9	2[a]
Definite	8	2	8	2
Probable	0	0	1	0
Asymptomatic infection	9	11	9	11
Total	17	13	18	13

NOTE. Data are no. of subjects. AS04, aluminum hydroxide and 3-*O*-desacyl-4'-monophosphoryl lipid A; ATP, according to protocol; gp350, glycoprotein 350; ITT, intention to treat.

- Vaccine did not prevent EBV infection, because gp350 antibodies only prevent infection of B cells, not epithelial cells!

Second generation vaccine candidates should include gp350 plus an EBV antigen which elicits antibodies that neutralize epithelial cell infection

1 Sokal et al 2007 *J. Infect. Dis.*

Development Landscape – Prophylactic EBV Vaccine Candidates

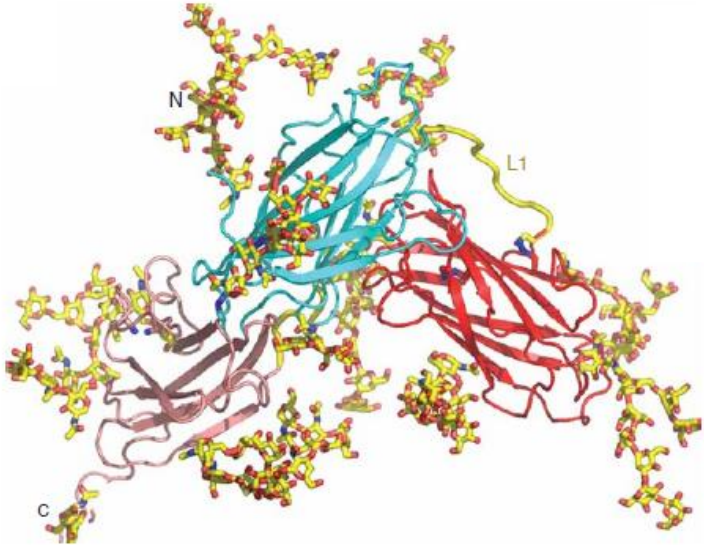
Currently in development

Company	Phase	Platform	Antigens	Comments
Moderna	1	mRNA LNP	gp220, gH/gL/gp42	Phase 1 started Dec 2021
NIH	1	Subunit nanopart.	gp350	Phase 1 started May 2022
ModeX	Preclin.	Subunit nanopart.	gp350, gH/gL±gp42	In-licensed from the NIH. Clinical entry expected in 1H2023.
Valneva	**Preclin.**	**Subunit**	**gp350, gH/gL, gB**	**incl. exclusive evaluation of third-party designs**

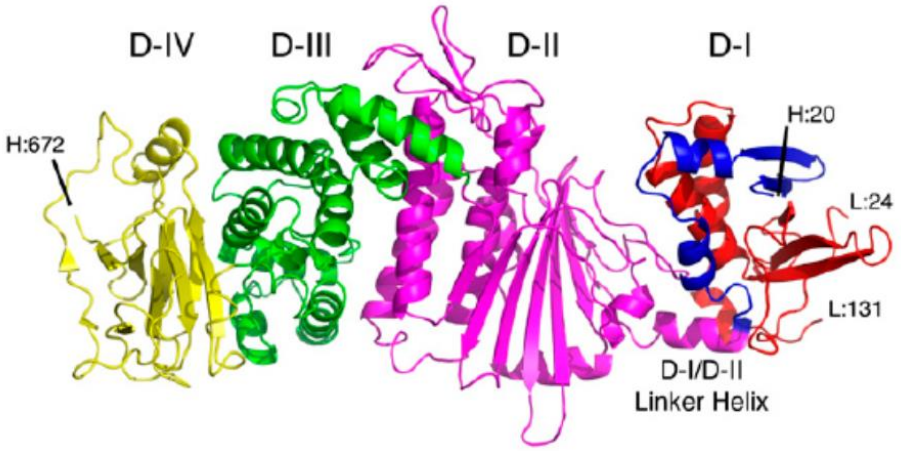
Valneva's Proposition: an Adjuvanted Subunit Protein Vaccine

Rational designs based on antigen structures

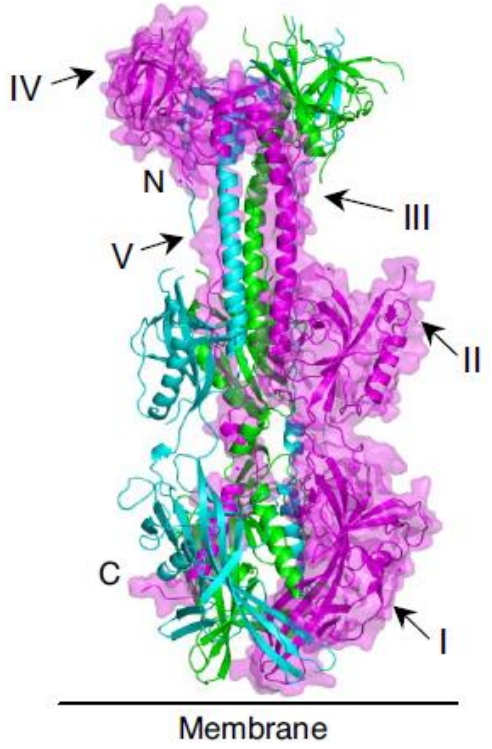
gp350 receptor binding domain[1]



gH/gL ectodomain[2]



gB ectodomain in postfusion conformation[3]



- Valneva is utilizing structural information to design gp350, gH/gL, and gB antigens
- We are in parallel evaluating third party antigen designs under exclusive evaluation license
- The best combination of antigens will be combined with an adjuvant in the final vaccine candidate

1 Szakonyi et al 2006 *Nat. Struct. Mol. Biol.;* 2 Matsuura et al 2010 *Proc. Natl. Acad. Sci. USA;* 3 Backovic et al 2009 *Proc. Natl. Acad. Sci. USA*

EBV Vaccine

Summary

- Neutralizing antibodies block EBV infection of B cell and epithelial cells
- Valneva's EBV vaccine candidate is based on adjuvanted, subunit viral glycoproteins for eliciting high titers of EBV-neutralizing antibodies
- Evaluation of external and internal antigen designs is ongoing
- The vaccine candidate will comprise the combination of antigens from these approaches that best neutralize infection of both epithelial cells and B cells
- The vaccine candidate will ultimately be produced in CHO cells using standard filtration and chromatography methods
- The addition of an adjuvant to further optimize immune responses will be investigated prior to development

Valneva Commercial Products

Peter Bühler

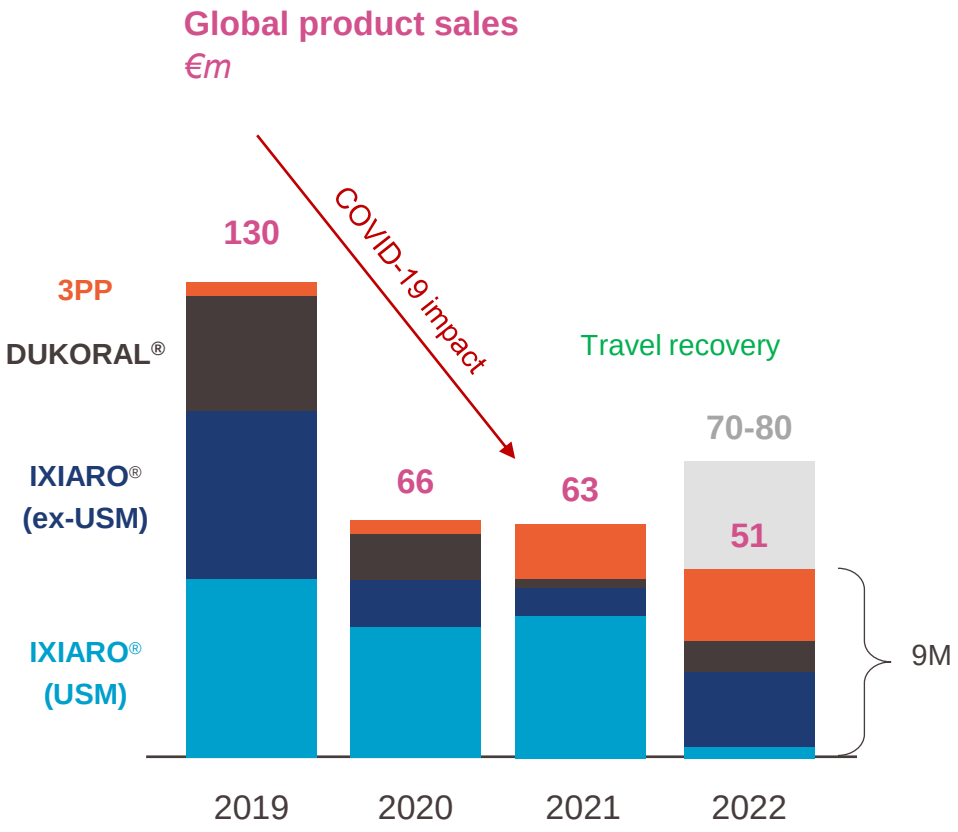
Current Commercial Portfolio

	Brand	Indication*	Partner / Year		Valneva commercial rights & key markets
Proprietary	IXIARO®	Active immunization against **Japanese encephalitis** from 2 months of age		**Global Rights**	**Valneva direct markets** : US, CA, UK, FR, Nordics, BE, NL, AT **Key markets addressed by Partners**: DE, AU, IL
	DUKORAL®	Active immunisation against **Cholera and ETEC** from 2 years of age**		**Global Rights**	**Valneva direct markets** : CA, UK, FR, Nordics, AT **Key markets addressed by Partners**: DE, AU, IL, PL
3rd-Party Distribution	FLUAD® FLUCELVAX®	Active immunization against **Flu**	Seqirus A CSL COMPANY	**2016**	Rights licensed from **Seqirus** in **Austria**
	KamRAB	Passive, transient **post-exposure** prevention of **rabies** infection	KAMADA	**2018**	Rights licensed from **Kamada** in **Canada**
	Rabipur®	Active immunization against **rabies in individuals of all ages**	BAVARIAN NORDIC	**2020**	Rights licensed from **Bavarian Nordic** in select markets: **CA, UK, FR, BE, NL, AT**
	Encepur®	Active immunization against **tick-borne encephalitis in adults and children**			Rights licensed from **Bavarian Nordic** in select markets: **Austria & France**
	PreHevbri	Active immunization against **hepatitis B virus in adults**	VBI VACCINES	**2022**	Rights licensed from **VBI** in select markets**:** **UK, Nordics, Netherlands, & Belgium**

*Please refer to Product / Prescribing Information (PI) / approved in your respective country for complete information about this vaccine. **ETEC indication in some markets only

Non-COVID Product Sales: Strong Growth Anticipated, Driven by Recovery of Travel Segment and Performance of 3rd Party Products

Travel Expected to Recover to Pre-COVID-19 Level by 2024[1]



DRIVERS

+ Pent-up travel demand
+ Re-establishment of Travel Medicine clinics/ramping up of resources
+ Elevated concern of infectious diseases amongst travelers
+ Increased troop deployment to Asia

BARRIERS

+ Airline capacity/staff shortages
+ Slowing economic growth and rising inflation
+ Impact of new COVID-19 waves
+ Strong demand led to temporary supply constraints in the later part of 2022; expected to be resolved in 2023

1 IATA/ Tourism Economics (July 2022)

Commercial Portfolio: Strong Sales Performance of €74.4 Million in the First Nine Months of 2022

Nine-Month 2022 product sales outside of COVID-19 grew by 11.2% vs. prior period

Significant recovery in travel markets

- Product sales of the **Japanese encephalitis vaccine** in the travel market increased to €19.4 million compared to €4.6 million (9M 2021)
- Product sales of the **Cholera vaccine** increased significantly to €9.2 million compared to €0.5 million (9M 2021)
- **Third-party product** sales increased to €18.4 million from €11.2 million (9M 2021), driven by growth related to Valneva's distribution agreement with Bavarian Nordic
- Strong growth offset by IXIARO® sales to U.S. Department of Defense of €3.5M vs €29.1M (9M 2021); expect new supply contract in 2023

COVID-19 vaccine sales

- The **COVID-19 vaccine** generated sales of €23.9 million
- Deliveries to EU member states who participated in the APA
- Supply of Valneva's COVID-19 vaccine to Bahrain

Executing Our Commercial Strategy

Three Key Levers to Accelerate Commercial Performance

Travel health recovery

Customer engagement through Valneva Travel Health

- Building brand identity
- Elevate Valneva's reputation as a committed travel health partner for HCP and travelers
- Provide tools and services to customers supporting acceleration of travel health recovery

valneva TRAVEL HEALTH

Expand vaccine portfolio

Evaluation of new in-licensing and product acquisitions

Distribution partnerships in selected regions

- Bavarian Nordic for Rabies and TBE vaccines
- Seqirus for flu vaccines
- Kamada for Rabies IgG
- VBI for Hep B vaccine
- Adding complementary distribution partnerships

VLA1553 launch preparedness

Evolution of commercial infrastructure

- Optimize commercial infrastructure to support launch excellence
- Market access/ recommendations
- Market and brand development

Valneva's Commitment and Leadership in Travel Health

Customer engagement through Valneva Travel Health

Recently launched above-brand identity demonstrates our dedication and commitment to supporting HCPs and travelers through:

- Our unique range of travel vaccines
- A strong R&D focus resulting in a promising pipeline of vaccines against infectious diseases with high unmet medical needs
- Our commitment to elevate the importance and awareness of travel health
- Providing HCPs educational programs, patient materials and relevant support services

The Evolution of the COVID-19 Program and Focus on the Future

- Manufacturing was suspended in the third quarter of 2022, but a limited number of clinical trials will continue to run into 2023
- As the program winds down, Valneva aims to deploy approximately eight to ten million doses of remaining inventory into international markets
- Continuing discussions with governments around the world, but current forecasts have not included any additional VLA2001 sales outside of current supply agreements
- Current shelf life recently extended to 18 months and Valneva is working to gradually extend to at least 24 months

Financial Overview

Peter Bühler

Company is Well Capitalized to at Least 2024

Balance sheet strengthened by successful capital raises

May 2021: U.S. Initial Public Offering with gross proceeds of $107.6 million

2021-2022: Follow on offerings and debt financing

- Most recent upsized Global Offering brought in €102.9 million in gross proceeds; led by new U.S. investor, with strong support from existing holders in the U.S. and Europe
- Increased the principal amount of existing debt financing agreement[3]

June 2022: €90.5 ($95) million investment by Pfizer[3] to support Valneva's contribution to Phase 3 trial of VLA15

Cash position of €261 million (Sept 30, 2022[1])

- Excludes proceeds received in October 2022 from upsized global offering[2]

Nasdaq: VALN – Euronext Paris: VLA

1 Valneva Reports Nine-Month 2022 Results and Provides Corporate Updates; 2 Valneva Announces Pricing of €102.9 Million Global Offering of American Depositary Shares and Ordinary Shares 3 Valneva Announces Upsized Financing Arrangement with Leading US Healthcare Funds Deerfield and OrbiMed; 4 Valneva and Pfizer Announce Closing of Equity Investment

Resource Optimization to Ensure Continued Growth

Strategic re-sizing of operations in conjunction with COVID-19 wind-down is currently underway

- Expected to result in a reduction of ~20-25% of existing workforce for annualized financial savings of approximately €12 million

Focused on the future

- Post restructuring, the Company's workforce is expected to be ~25% above pre-COVID levels enabling the Company to retain talents and expertise to successfully execute on its strategy

- Re-sizing will allow the Company to increase efficiency and focus on its operational and strategic business objectives:
  - Advance our chikungunya vaccine candidate towards marketing approval and launch
  - Complete the Phase 3 trial of our Lyme disease vaccine candidate
  - Progress select pre-clinical assets
  - Focus on strengthening our clinical pipeline

Valneva is Poised for Substantial Growth

Led by potential new product launches

Additional growth drivers:

- Continued recovery of travel market to “pre-COVID” levels and beyond
- New U.S. DoD contract for IXIARO; expected 2023
- Further expansion of 3rd-party distribution segment
- Potential in-licensing or acquisition of additional clinical and/or commercial-stage product(s)

Valneva 2022 Financial Guidance

Expected total revenues of €340 to €360 million, including:

- €30 to €40 million of COVID-19 vaccine sales; ongoing efforts to sell existing inventories will run into 2023
- €70 to €80 million of other vaccine sales
- Approximately €240 million of other revenues, primarily driven by revenues recognized from EC and UK COVID-19 contracts

Lower R&D expenses of €95 million to €110 million expected compared to €120 million to €135 million previously

- Reflects phasing of clinical trial expenses and accelerated wind-down of VLA2001-related activities

Q&A Session

Significant Catalysts and Expected News Flow

Overview

Program	Milestone	2022	2023		2024		2025
		Q4	H1	H2	**H1**	H2	
VLA15 Lyme disease	Antibody persistance data	✓		✓			
	Phase 3 enrollment completion		✓				
	Primary efficacy readout, two tick seasons					✓	
	BLA and MAA filings						✓
VLA1553 Chikungunya virus	Antibody persistence data	✓		✓		✓	
	BLA Submission completion	✓					
	Adolescent study enrolment completion		✓				
	Adolescent data			✓			
	Ex-U.S. regulatory submissions			✓			
	Potential FDA approval			✓			
	Potential PRV sale			✓			
	ACIP recommendation/vote				✓		
	Potential ex-U.S. approvals				✓	✓	
COVID-19	Additional data (follow-up, elderly, booster)			✓	✓		
	Potential label extensions				✓		
Other pipeline programs	hMPV initial PoC / potential clinical entry	✓				✓	
	Zika potential clinical entry			✓			
	EBV initial PoC / potential clinical entry			✓			✓
	Next preclinical candidate PoC					✓	

Achieving our Strategic Vision

Becoming the leading specialty vaccines company

Applying our proven capabilities in development, manufacturing and commercialization of vaccines

to make a real, positive impact on people's lives by addressing unmet needs in infectious diseases