Developing a vaccine against Lyme disease (VLA15)

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Valneva, a fully integrated, commercial stage biotech company developing innovative vaccines

Products

Commercial products
+ Valneva expects total revenues of €105-115m in 2017, coming mainly from its two proprietary travel vaccines

Portfolio

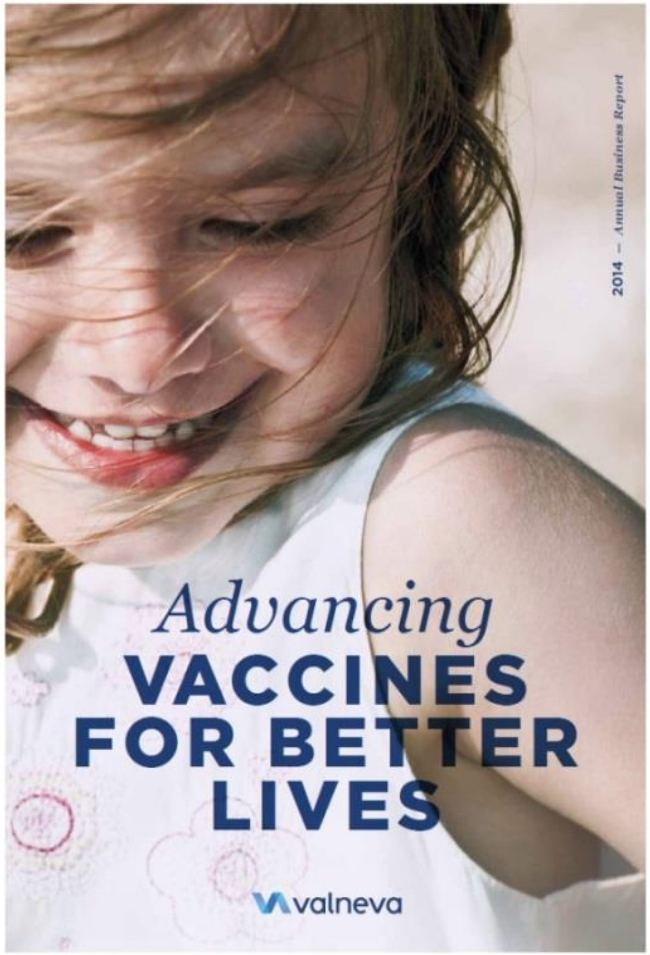
Vaccine candidates
+ Valneva invests in innovative R&D programs in areas of unmet medical needs
+ Lyme Phase I + others @ Phase I entry (e.g. Chik, Zika)

Platforms

Technologies & services
+ Valneva offers unique technology platforms (EB66®, IC31®) and services to a broad range of clients

Partnering

Product partnering & licensing
+ Valneva creates near and long-term value through partnering of vaccine candidates
+ C.Difficile (Ph III ready) sought to be partnered in 2017



Lyme Disease
Key facts

- Tickborne disease – *Ixodes scapularis* predominant in Eastern U.S. *Ixodes ricinus* in Europe
- Caused by *Borrelia burgdorferi* spirochete – resides in gut of tick, migrates to salivary gland and enters host during tick feeding
- Early symptoms – fever, headache, fatigue, erythema migrans rash (70-80%), arthralgia, myalgia
- Left untreated, can spread to joints (arthritis), heart (carditis), and cause neurological problems
- Diagnosed by clinical symptoms, exposure to known endemic area, and lab tests

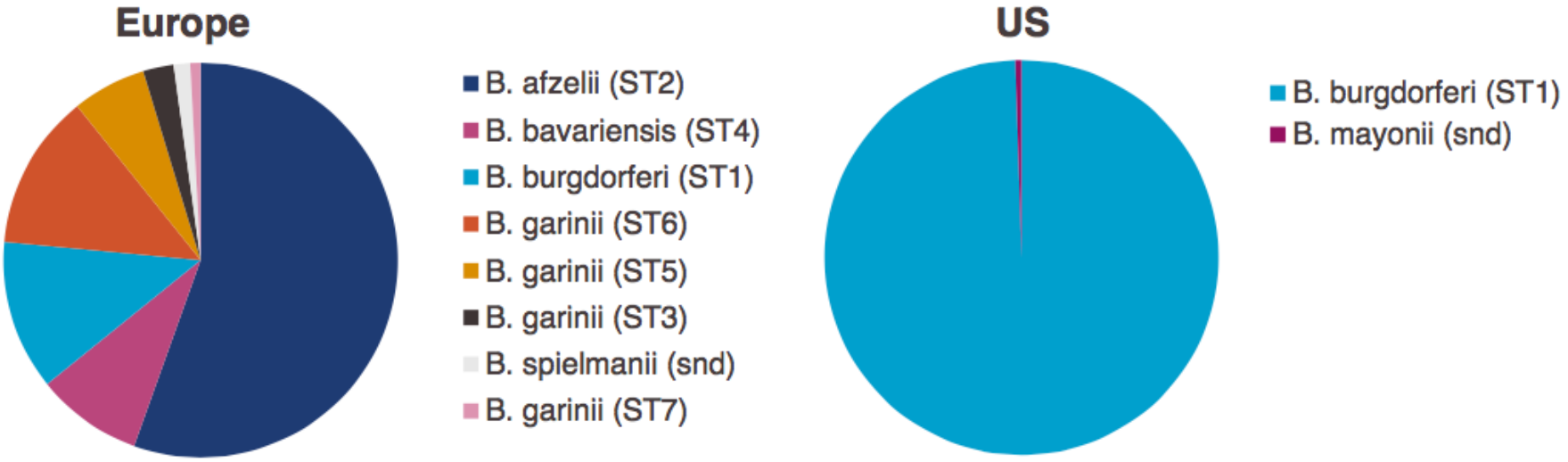
  Treatment: Antibiotics (doxycycline, amoxicillin, or cefuroxime axetil)

Plotkin 2016

Lyme Disease – Epidemiology

Prevalent Strains in the US & Europe

- **Analysis of US CDC statistics** and 595 European* (16 countries) LB-patient isolates**
  - US: LB is caused almost exclusively by *B. burgdorferi* s.s. (ST1)
    - The novel species *B. mayonii* rarely causes LB in US*** (prevalence and incidence to be watched)
  - Europe: *B. afzelii* (ST2) is the most common causative agent of LB
    - *Borrelia* belonging to OspA ST1 to ST6 are responsible for almost all European LB cases



* Data from German National Reference Centre for *Borrelia* at the Bavarian Health and Food Safety Authority (Germany) and Baxter have been summarized.
** Centers for Disease Control and Prevention. *** Pritt et al., Lancet. Infect. Dis. 2016. Snd; Serotype not determined

Lyme Disease Progression
Stages

- Stage I (early localized infection)
  - 3-30 days after tick bite
  - Erythema Migrans (EM) (60-90% of patients)
  - Nonspecific flu-like symptoms (muscle soreness, fever and malaise)
- Stage II (early disseminated infection)
  - Days or weeks after initial infection
  - Borrelial lymphocytom (Europe), rheumatologic and cardiac involvement
  - Neuroborreliosis (10-15% of patients)
- Stage III (late “persistent” infection)
  - After several months or years without treatment or without adequate treatment
  - Chronic neurological symptoms (5% of patients)
  - Lyme Arthritis (USA) (10% of patients)
  - Acrodermatitis chronica atrophicans (Europe)

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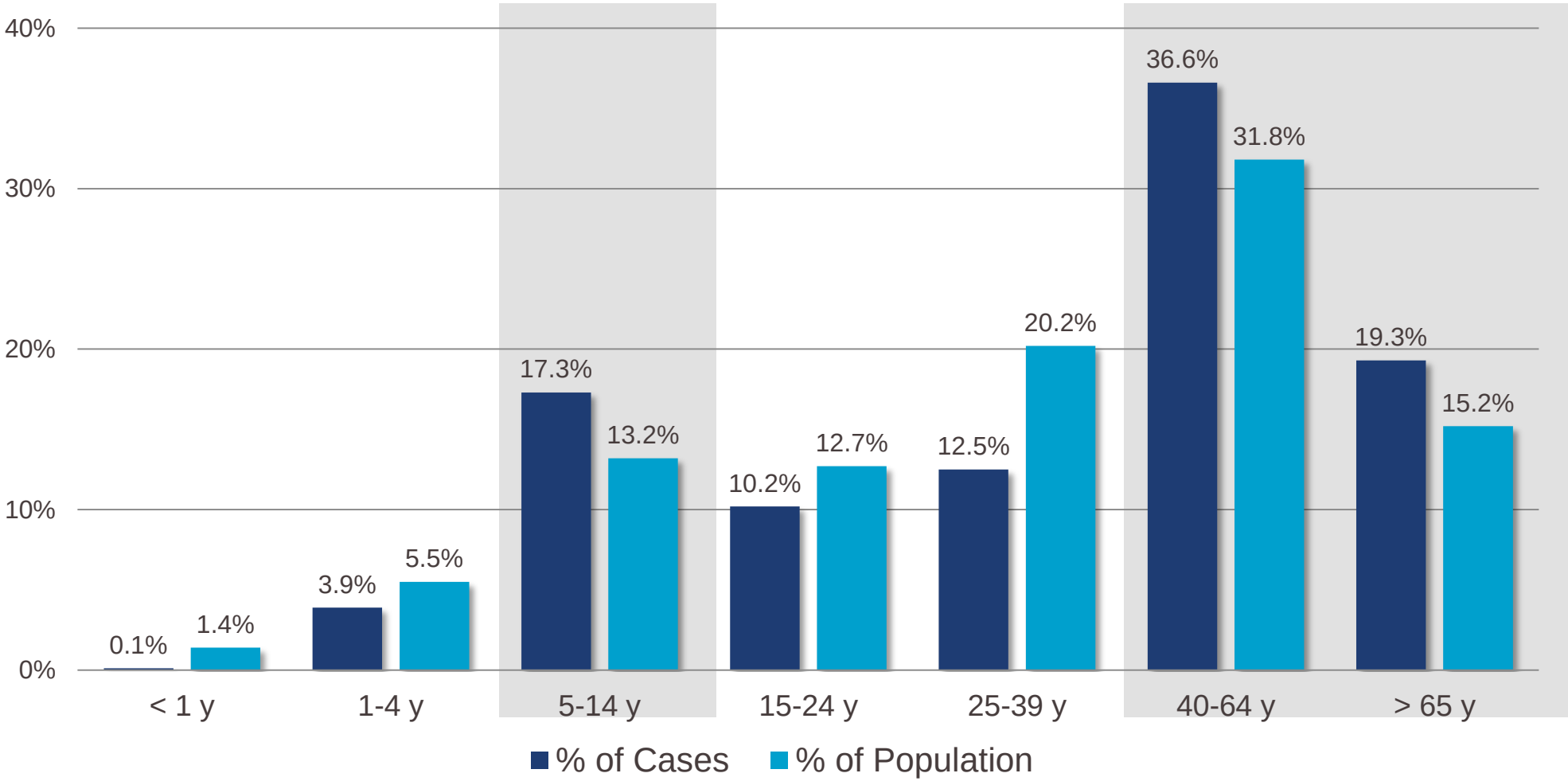
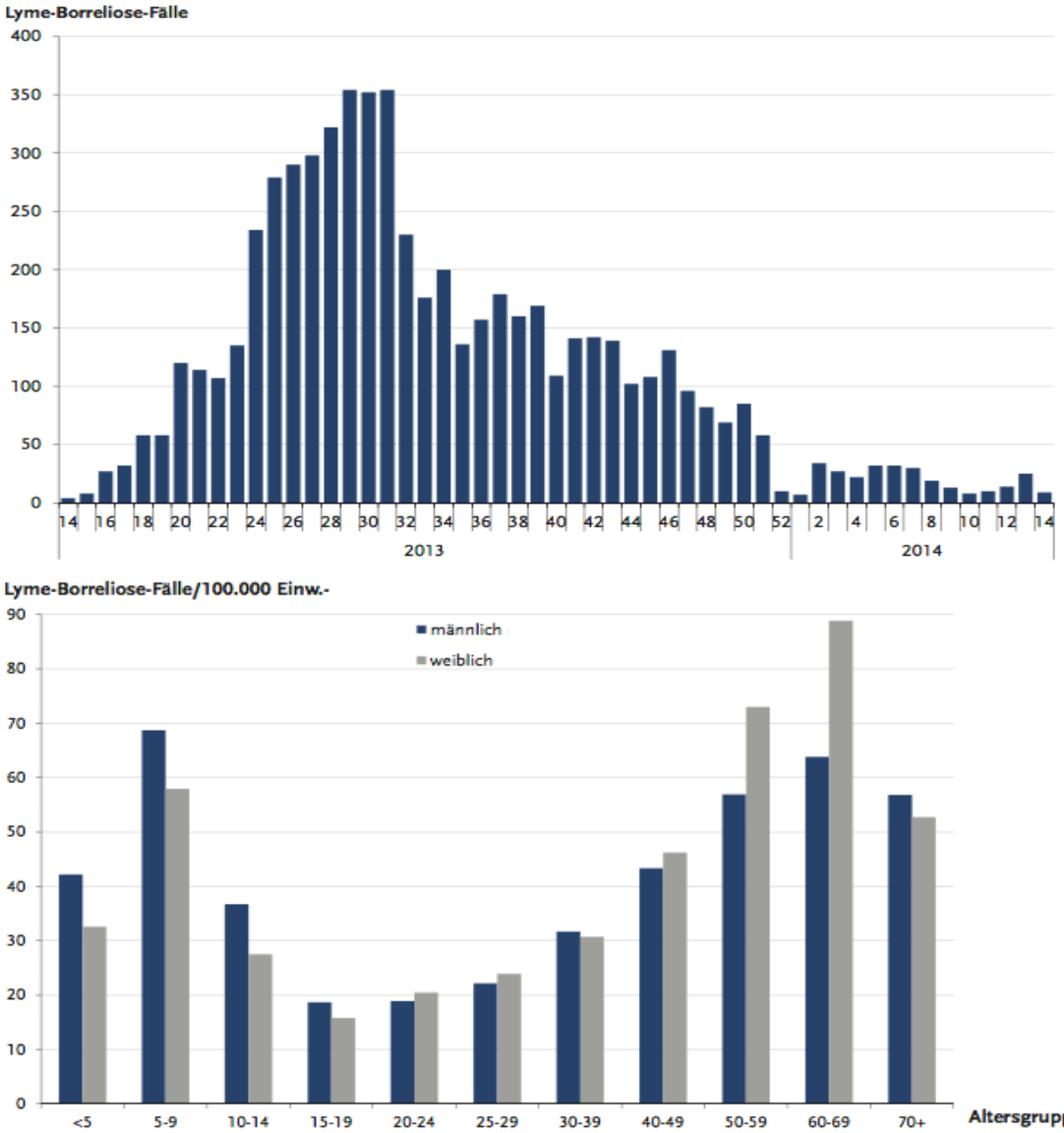
Lyme Disease
Cases by Age (US)



Sources: MMWR, published Oct 2016, Number of reported cases of notifiable diseases 2014, US Census 2017 projection

Lyme Disease

Europe



RKI (2015) – Bavaria 2013/4

- Lyme borreliosis cases are reported throughout the year with majority of cases during spring and summer
- The distribution in various age groups show 2 peaks
  - at 5-9 years
  - at 50-70 years
- In younger age groups more cases are seen in males, in the older age groups in females

We should have a Lyme vaccine…

Because:

- Untreated LD can lead to fever, rash, facial paralysis, severe arthritis-like joint and muscle pain, brain inflammation, and heart problems
- Most common vector borne illness in the Northern Hemisphere (>300,000 cases per year in US[1] and >200,000 cases per year in Europe[2])
  - 7th most prevalent notifiable disease (US)
  - Estimated 329,000 new Lyme disease cases per year in the US[1]
  - Another recent study postulates up to 444,000 cases in the US[1]
  - Cases have more than tripled in last 20-years
- Direct medical costs in the U.S. estimated up to $1.3 billion[3]
- Vaccination with OspA was proven to work in the 1990s
- Other preventive measures have not been show to work on a public health scale

Sources: **1** Latest data from the CDC (PR on Aug 19, 2013); **2** Estimated from available national data. Case reporting is highly inconsistent in Europe and LB infections still go undiagnosed, based on WHO Europe Lyme Report; **3** Adrion, E, et al PLOS ONE Feb 2015

History of Lyme Vaccines

Vaccination with OspA has been proven in the past

- Efficacy of two OspA (ST-1) based vaccines in the 1990‘s:
  - › LYMErix (licensed in 1998, withdrawn from market in 2002): Vaccine efficacy (symptomatic LD):
    49% in 1st year, 76% in 2nd year
  - › ImuLyme: Vaccine efficacy (symptomatic LD): 68% in 1st year, 92% in 2nd year
- Postulate that OspA vaccines might induce antibiotic-refractory Lyme arthritis due to molecular mimicry of OspA and human LFA-1* epitopes was disproved for LYMErix
  - › Postulate withdrawn in 2011[1]
    - FDA Panel concluded no evidence for association between vaccine and arthritis.
    - No difference of arthritis incidence seen in vaccinated subjects versus unvaccinated subjects in a post-licensure VAERS study (after 1.4 million distributed doses) and a Phase 4 safety study
      (2,568 vaccinated subjects vs 7,497 control subjects)
    - Later, FDA retrospective review of all safety data concluded no safety signal.
- Mechanism of action of OspA based vaccines well understood

(Lathrop et al, Vaccine 2002)
* Leucocyte Function.associated Antigen ; 1 A.C. Steere et al. CID 2011:52 (Suppl 3) S259

Anti-OspA Protective Response

Mode of Action

Step 1	Step 2	Step 3	Step 4
Vaccine, when injected, elicits high levels of anti-OspA antibodies	Tick attaches to vaccinated human and begins blood meal (24- to 48-hour attachment needed to transmit *B. burgdorferi)*	Anti-OspA antibodies from vaccinee enter tick	Antibodies kill *B. burgdorferi* in midgut, preventing transmission to human host

A Vaccine against Lyme Disease

The “ideal” Target Product Profile …

The target is a Lyme disease vaccine that prevents strains prevalent on both sides of the Atlantic, is well tolerated, lacks epitopes that would hypothetically cross-react with human proteins, is licensed for use in children, and provides at least 80% efficacy for 2 years.

Prof. Stanley A. Plotkin: Need for a Lyme Disease Vaccine, N Engl J Med 375;10, 2016

Valneva‘s Lyme Vaccine Candidate (VLA15)

A new hexavalent OspA based vaccine candidate

- Currently in Phase I (US and Europe)
- Only active clinical vaccines program to date / No vaccine currently on the market
- Multivalent, protein subunit- based vaccine – intended for global reach
- Expected for > 2 yrs of age
- Vaccine Targets the outer surface protein A (OspA) of Borrelia
  - › In vaccines design epitope with homology to hLFA-1 eliminated

Source picture: PHIL – Public Health Photo Library.

Protection of VLA15 immunized mice

Challenge after **active** immunization

- Mice were immunized three times s.c. at days 0, 14 & 28
- Challenge was performed two weeks after last immunization
- Infection was determined by VlsE ELISA and qPCR for OspA (ear biopsy)

Immunization		Infected/Total				
		Tick challenge			Needle challenge	
Immunogen	Dose	B. burgdorferi (ST1)	B. afzelii (ST2)	B. bavariensis (ST4)	B. garinii (ST5)	B. garinii (ST6)
Placebo	-	13/19	17/17	12/15	9/9	0/10
VLA15	3 µg	1/13***	1/13***	0/11***	1/10***	0/10***
VLA15	0.3 µg	1/21***	0/14***	0/16***	0/10***	2/10***
VLA15	0.03 µg	8/20^{ns}	3/15***	0/9***	3/10**	3/10***
VLA15	0.003 µg	12/21^{ns}	8/13*	2/11**	7/9^{ns}	6/10^{ns}

- **VLA15 induces significant protection at a 0.03 to 3 µg dose when challenged with 5 different Borrelia OspA serotypes**

P-values were calculated with Fisher's exact test (two tailed); * <0.05, ** <0.01 and *** <0.001.; ns, non-significant; Comstedt et al. 2017, PLoS One under review

Protection of VLA15 immunized mice
Challenge after **passive** immunization

- Mice were immunized i.p. one day prior to challenge
- Challenge was performed as for active immunization experiments
- Infection was determined by VlsE ELISA and qPCR for OspA (ear biopsy)

Immunization		Infected/Total				
		Tick challenge			Needle challenge	
Immunogen	Dose	B. burgdorferi (ST1)	B. afzelii (ST2)	B. bavariensis (ST4)	B. garinii (ST5)	B. garinii (ST6)
Placebo	-	11/17	20/20	6/6	8/10	8/10
VLA15	200 µL	1/16***	1/19***	1/8**	0/10***	0/10***
VLA15	140 µL	0/18***	3/18***	0/2^{ns}	1/10***	0/10***
VLA15	80 µL	1/16***	6/19***	0/6**	3/10^{ns}	0/10***
VLA15	20 µL	9/19^{ns}	12/19**	2/5^{ns}	4/10^{ns}	0/10***

- **Sera from VLA15 immunized mice provide dose-dependent, significant protection when challenged with 5 different Borrelia OspA serotypes**

P-values were calculated with Fisher's exact test (two tailed); * <0.05, ** <0.01 and *** <0.001.; ns, non-significant; Comstedt et al. 2017, PLoS One under review

Generation of OspA Serotype Specific Monoclonal Antibodies

Mouse and human mAbs generated

Mouse anti-OspA serotype specific monoclonal antibodies

- Mice were immunized with full-length OspA serotypes 1 to 6
- mAb producing hybridomas were selected for specific reactivity with the respective OspA serotype & counter-selected for reaction against the remaining five OspA serotypes
- A single mAb per OspA serotype has been converted to chimeric mAb, with a human IgG1 Fc domain
  - › Use as internal control in clinical ELISA

	Mouse mAb					
Coating antigen	**OspA ST1**	**OspA ST2**	**OspA ST3**	**OspA ST4**	**OspA ST5**	**OspA ST6**
OspA ST1	1.49	0.11	-	-	-	-
OspA ST2	0.06	1.58	-	-	-	-
OspA ST3	-	-	1.51	-	-	-
OspA ST4	-	0.07	-	1.62	-	-
OspA ST5	-	-	-	-	1.64	-
OspA ST6	-	-	-	-	-	1.15

- Specific mAbs were selected successfully against all six OspA serotypes

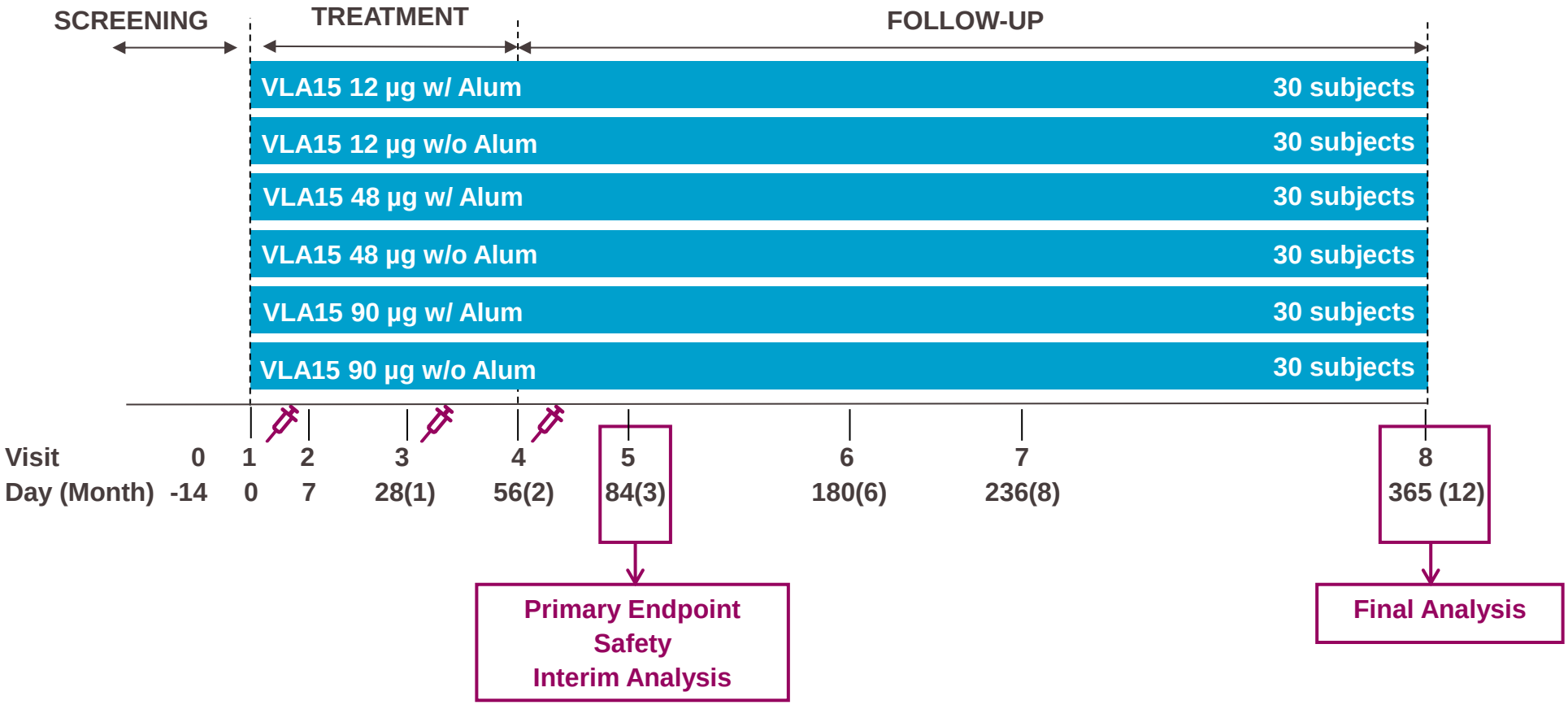
Unpublished data, Valneva

Lyme Vaccine Candidate (VLA15) Phase I (VLA15-101)

Observer-blind, partially randomized, dose escalation study

Phase I study to be conducted in US and EU

- 6 groups, 3 doses, 2 formulations
- 180 subjects aged 18-<40 years
- Primary objective: Safety and tolerability to Month 3
- Secondary objectives: Safety and tolerability until M12; Immunogenicity



A Vaccine against Lyme Disease
Conclusion

- There is a strong need for vaccination against Lyme disease both in the US and Europe

- Lymerix was a scientific success confirming that Lyme is a vaccines preventable disease, but a public relations fiasco

- VLA 15 is a modern vaccine candidate which provides all necessary characteristics for a new multivalent OspA vaccine

Thank you
Merci
Danke
Tack

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