SARS-CoV-2 vaccine development
Valneva's project VLA2001

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valneva

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Valneva's Value Proposition

Integrated business model with valuable commercial and R&D assets

R&D

Lyme vaccine in Phase 2; data read out from July; strategic collaboration with Pfizer announced April 2020[1]

US/EU market opportunity of ~$1bn per annum

- Only program in clinical development
- Pfizer to lead late-stage development and drive commercialization

Chikungunya Phase 3 to commence Q4 2020

Global market opportunity of ~$0.5bn per annum

- Huge synergy with existing infrastructure
- Possible Priority Review Voucher upside

R&D provides upside for shareholders
Two unique vaccines with low R&D risk profile

Commercial Business

Total sales revenues €129.5m in 2019; +25% vs. 2018

IXIARO®

- Only licensed JE vaccine for travelers in US CAN, EU; mandatory for US Military
- Sales > €90m in 2019

DUKORAL®

- Cholera (LT-ETEC) vaccine, licensed in CAN, EU, ROW
- Sales > €30m in 2019

Recent transactions underline major valuation disconnect
BN product acquisition from GSK @ 4.5x revenue

1 Valneva PR: Valneva and Pfizer Announce Collaboration to Co-Develop and Commercialize Lyme Disease Vaccine, VLA15

Valneva: A specialty vaccine company focused on prevention against diseases with major unmet needs

> 500 people

Four main sites
Six in-market commercial teams

Valneva's Broad Vaccine Clinical Trial Experience*
Summary

- **Ran more than 40 Phase 1 & 2 studies and 15 Phase 3 & 4 studies**
- **Experience in more than six disease areas (tropical diseases, nosocomial infections, influenza, hepatitis C, respiratory, diarrheal, Lyme ..)**
- **Prophylactic and therapeutic vaccine approaches**
- **Different routes of application (i.m., s.c., intradermal, oral, topical etc.)**
- **Experience with study populations from 2 months to 85 years of age and in study populations from healthy adults to ICU patients**

* incl. predecessor Intercell

Clinical target product profile of vaccines against Covid-19
Key considerations

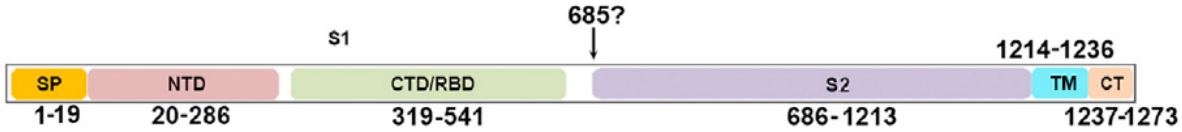
- **Immunogenicity/efficacy**
  - Induction of sustainable protection with rapid onset for use during outbreak in a broad population
  - Protection in the population at risk for severe or lethal diseases

- **Safety profile**
  - Acceptable risk - benefit profile

Vaccines solutions are needed as herd immunity will probably not be achieved by natural infections and treatments are not in sight

VLA2001 – SARS-CoV-2 inactivated vaccine
Similarity with other Coronaviruses

- **Coronaviruses**
  - › High similarity between SARS-Cov and SARS-CoV-2
  - › MERS and other Coronaviruses show limited identity only
  - › Lowest level of identity with Alpha-Coronaviruses
  - › Highest level of identity in S2 domain of S protein



S protein **

Percentage amino acid identity of coronavirus spike and nucleocapsid proteins with SARS-CoV-2 proteins*

Virus type	*Virus*	*Nucleocapsid*	*S*	*S1*	*S2*	*S1^A*	*RBD*
Betacoronavirus	SARS-CoV	90	77	66	90	52	73
	MERS-CoV	49	33	24	43	ND	ND
	HCoV-OC43	34	33	25	42	ND	ND
	HCoV-HKU1	34	32	25	40	ND	ND
Alphacoronavirus	HCoV-229E	28	30	24	35	ND	ND
	HCoV-NL63	29	28	21	36	ND	ND

*Okba et al. 2020, Emerg Infect Dis 26, early release; **, Wang et al., 2020, Cell 181, 1–11.

VLA2001 – SARS-CoV-2 inactivated vaccine
Cross-reactivity with other Coronaviruses

- **X-reactivity with SARS-CoV-2**
  - Limited cross-neutralization activity shown between SARS-CoV & SARS-CoV-2 *
  - Strong cross-neutralization activity expected vs circulating SARS-CoV-2 strains

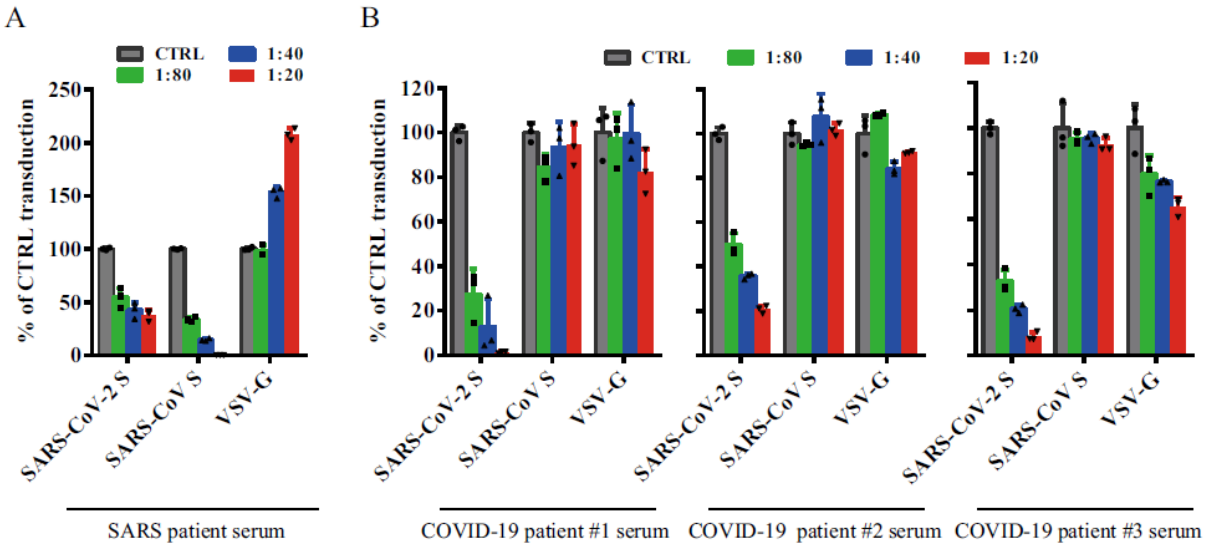


Fig. 6 Limited cross-neutralization of SARS and COVID-19 sera. All sera were incubated on 56 °C for 30 min to eliminate complement. SARS-CoV S and SARS-CoV-2 S pseudovirons were pre-incubated with serially diluted SARS patient serum (**a**) or COVID-19 patient sera (**b**) for 1 h on ice and then added on 293/hACE2 cells. Pseudoviral transduction was measured 40 h later. Experiments were done in triplicates and repeated twice, and one representative is shown. Error bars indicate SEM of technical triplicates. Source data are provided as a Source Data file.

- **X-reactivity among Coronaviruses ****
  - Related Coronaviruses share epitopes that can elicit x-reactive and x-neutralizing antibodies
  - Only one study showing x-neutralizing activity between MERS and SARS-CoV (low titers); otherwise only x-neutralizing activity shown for closely related animal CoVs

*Ou et al. 2020, Nat Commun 11:1620, doi.org/10.1038/s41467-020-15562-9; **, Meyer et al. 2014, Virus Res 194:175-83.

SARS-CoV-2 vaccines
A view on different approaches

Pace to clinical proof

Fast Manufacturing at scale

Inactivated vaccines	Nucleid acid vaccines
▪ Traditional technology - many licensed vaccines using this platform ▪ Clear regulatory path (No GMO, No foreign vector) Can be produced at high purity and large scale – significant global manufacturing capability Antigen: Whole virion inactivated vaccine (Sinovac Biotech / Wuhan Institute Biol Products) (ongoing trials) / Valneva) Adjuvants Alum or CpG 1018	▪ Relatively easy and fast manufacturing process ▪ So far no preventive vaccines for human use on the basis of RNA or DNA has been licensed – only in clinical trials Antigen: Spike protein of SARS-CoV-2 **DNA** - Electroporation needed for application (Inovio) **mRNA** in lipid particles (Moderna), (CureVac) **BioNTech use three different RNA platforms in lipid particles** - uridine RNA, modified RNA , self-amplifying Antigens: Modified Spike protein SARS-CoV-2 or only the receptor bindings domain (RBD)
Recombinant vaccines	**Vector based vaccines**
▪ Recombinant vaccines considered a well established approach and technology Antigens: Recombinant expressed viral S protein or Recombinant expressed chimeric viral S, N1 and N2 protein with LTB (chimeric LTB part of the protein as adjuvants) (MIGAL / MegVax – Oral application) Adjuvanted (Matrix-M adjuvant (saponin-based) (Novavax)) „Molecular clamp“ technology (trimerization to enhance antigenicity) (Queensland) + Adjuvants CpG or AS0X / (GSK/ Sanofi)	▪ Already existing licensed vaccines (Ebola, MVA) or candidates in licensing (Adeno) Antigens: Spike protein of SARS-CoV-2 or subdomains **Adenovirus vector -** Replication-incompetent vector (E1 deleted), different types; Adenovirus type 26 vector used for Ebola vaccine (Janssen) **MVA vector -** Replication-incompetent vector - native, full-length SARS-CoV-2 spike protein **Measles vector -** live attenuated, replicating virus vector - native or a modified membrane-bound version of the SARS-CoV-2 spike glycoprotein

VLA2001 – SARS-CoV-2 inactivated vaccine

An inactivated SARS-CoV-2 vaccine is positioned to maximize chances of success

Inactivated vaccines in general:

- Inactivated viral vaccines were shown before to be highly effective in humans (e.g. JEV) in 2-dose regimen, generating long-lasting immune responses
- Inactivated vaccines in general have a very good safety profile
- Pre-clinical and clinical paths are straight forward in contrast to some of the other technologies applied for SARS-CoV-2 vaccines

Inactivated vaccines for SARS-CoV-2:

- An inactivated SARS-CoV-2 vaccine would be suitable for vaccination of the general population as well as risk groups (elderly, immuno-compromised, individuals suffering from other diseases)
- Inactivated SARS-CoV-1 vaccines were shown to be safe and immunogenic in animals (Baxter, Sinovac and others) and humans (Sinovac) *
- Inactivated SARS-CoV-2 vaccine adjuvanted with Alum (Sinovac) was shown to be safe and immunogenic in animals (mice, rats, NHPs) and clinical study will assess CpG 1018 as alternative adjuvant **

*Qin et al. 2006, Vaccine 24:1028-34; Spruth et al. 2006, Vaccine 24:652–61; See et al. 2006, J Gen Virol 87, 641–50; Roberts et al.2010, Viral Immunology 23:509–19; Lin et al. 2007, Antiviral Therapy 12:1107-13.

**Gao et al. 2020, bioRxiv preprint doi: https://doi.org/10.1101/2020.04.17.046375.

VLA2001 – SARS-CoV-2 inactivated vaccine
Summary

Vaccine design:

- SARS-CoV-2 grown on Vero cells (as used for IXIARO)
- Whole virus SARS-CoV-2 vaccine, highly-purified based on partially standardized process platform derived from IXIARO
- Inactivation by ß-propiolactone
- CpG 1018 and Alum adjuvanted as favoured formulation

Further development:

- Different adjuvants expected to be tested pre-clinically
- Only 1 formulation to be tested in Phase 1/2 - planned to be initiated still this year

VLA2001 – SARS-CoV-2 inactivated vaccine

Valneva's vaccine development update

- **Antigen:**
  - Valneva has obtained three SARS-CoV-2 strains (Institut Pasteur, France, European Virus Archive Global (EVAG) Italy, Med Uni Vie, Austria)
  - Generation of MVSB ongoing
- **Adjuvant:**
  - Valneva has obtained CpG 1018 adjuvant (Dynavax, contained in U.S. FDA-approved HEPLISAV-B vaccine
  - Discussions on MF59 access
- **Preclinical development:**
  - Valneva has re-activated its BSL3 lab capabilities at its R&D centers
  - Pre-clinical in-vivo experiments in mice will be performed in house to assess immunogenicity and possibly safety in mice
  - Pre-clinical in-vivo experiments in NHPs are planned to assess immune pathology and/or ADE in parallel to other pre-clinical development and Phase 1/2 study
- **Clinical material manufacturing:**
  - VERO based viral clinical manufacturing facility in Scotland will be adjusted to BSL3 (operational by mid of July)

Two novel adjuvants considered

Both adjuvants used in other commercially available vaccines

		CpG 1018	MF59		
Molecule/Target		Toll-like receptor 9 (TLR9) agonist	Squalene based oil-in-water emulsion		
Marketed products	**Vaccine**	**HEPLISAV-B**	**FLUAD**	**AFLUNOV/ AUDENZ**	**FOCETRIA/ CELTURA**
	Indication	Hepatitis B	Seasonal flu	H5N1 flu	H1N1 flu
	Completed Clinical Trials	10 ~14 000 patients	36 ~37 000 patients	18 ~13 000 patients	18 ~11 000 patients
	Market Approval	US: 2017 EU: pre-registration	US: 2015 EU: 1997	US: 2020 EU: 2010	US: 2009 EU: 2009
	Sales	35m$ (2019) Launched in 2018	~250m$* (2019)	Not available	~2,3b$ ~230mdoses (2009-2010)
Other products at clinical stage	**Indications**	HIV, CRC, NHL	HIV, CMV, RSV, Parvo B19, GroupB Steptococcus, Pneumococcal Infections, HCV		
	Past/Current Clinical Trials	4 ~160 patients	33 ~10 000 patients		
	Other comments	April 2020: Dynavax and Sinovac announced Collaboration to Develop a COVID-19 inactivated vaccine	*The safety profile of an MF59-adjuvanted vaccine is well established through a large safety database*** *Seqirus is already providing MF59® to teams researching coronavirus vaccines and is in discussions with governments and global health nonprofits about its potential use in other projects.****		

Sources: Globaldata, Clinicaltrial.gov, vaccines SPC, Novartis Annual Report 2009-2010

* https://www.csl.com/-/media/csl/documents/seqirus-president-presentation-to-the-macquarie-australia-conference-sydney-april-2019.pdf?la=en-us&hash=A11C651E54D4F95DF8F10E28E8EA0EF7F06E4C3D

*** O'Hagan DT, Expert Rev Vaccines. 2007 Oct;6(5):699-710. MF59 is a safe and potent vaccine adjuvant that enhances protection against influenza virus infection.*

*** https://www.seqirus.com/news/our-offer-to-help-battle-coronavirus

VLA2001 – SARS-CoV-2 inactivated vaccine
Pre-clinical studies

- **Immunogenicity studies in BALB/c mice**
  - Two s.c (or i.m.) immunizations 3 weeks apart
  - Assess immunogenicity 2 weeks post first, and 2 and 4 weeks post second immunization
  - Assess dosing of SARS-CoV-2 antigen
  - Assess benefit of adjuvant (Alum, CpG 1018, MF59)
  - Evaluate immunization route
  - Evaluate longevity of immune response (up to 26 weeks post 2nd immunization)
  - Assess safety in mice

- **Safety, efficacy and immunogenicity studies in NHPs (Dr Le Grand, CEA/UMR1184, Paris)**
  - Detail of the studies to be defined; see als study by Gao et al. 2020 *
  - Study performed in parallel to Phase 1/2 study
  - Assess efficacy against wild type SARS-CoV-2 challenge
  - Evaluate possible ADE of disease upon challenge
  - Evaluate animals for any immune or lung pathology

*Gao et al. 2020, Science May 6. pii: eabc1932. doi: 10.1126/science.abc1932.

Clinical Development Considerations – Early Stage

Subject to agreement with regulatory authorities

- Valneva plans for a Phase 1/2 study to rapidly progress the inactivated SARS-CoV2 vaccine candidate
- We anticipate clinical testing one formulation (virus+adjuvant) in 2 doses / 2 schedules
- Given the inactivated vaccine approach is well established and the adjuvants considered are licensed, a limited initial safety stage (I, N=20-50) is considered sufficient
- Further parallel study stages will deliver initial data in elderly subjects (Stage IIa, N=80-100) and robust data in younger adults (Stage IIb, N~1,200):
  - 300 subjects / dose group → sufficient to detect adverse events at a 1% rate
  - Sufficient sample size to provide exploratory efficacy data for pooled VLA2001 groups*
- We assume these data could be sufficient to support an Emergency Use Authorization

* For a putative 90% Vaccine Efficacy, 80% Power at a 2% Attack Rate; for a putative 70% Vaccine Efficacy, >90% power at a 5% Attack Rate

SARS-COV-2 Commercial Manufacturing Strategy

Assumptions and Estimated annual Antigen Bulk Production Capabilities

Process Summary

- BSL3 production of wild type strain
- Full disposable upstream and downstream process
- Fully-integrated, single-use disposable bioreactor (up to 600m² per reactor)
  - › Compact high-cell-density
  - › Multiple reactors can be operated simultaneously
  - › Linear scalability from R&D to manufacturing
  - › Low footprint and cost effective
- Viral inactivation by ß-propiolactone
- Efficient and modular downstream process: based on well established and scalable unit operations for Valneva's viral vaccines

Assumptions

- Harvest titer ≥7 log pfu/mL (published)
- Single harvest
- Process productivity 0.2 dose equivalent per cm²
- 2 reactors per facility operated simultaneously
- Upstream process duration: 14 days per reactor
- Up to 42 lots/year (21 per bioreactor) per facility

Annual production capacity

- Estimated 1.2m doses/lot
- **Total annual production capacity for existing facility: up to 50m doses***

  → Up to 200m doses for 2 facilities or up to 250m doses for 3 facilities*

*Provided that all potential available Valneva resources are fully dedicated to COVID-19

Thank you.

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