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

May 28, 2020
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**Valneva’s Value Proposition**
Integrated business model with valuable commercial and R&D assets

<table>
<thead>
<tr>
<th>R&amp;D</th>
<th>Commercial Business</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lyme vaccine in Phase 2; data read out from July; strategic collaboration with Pfizer announced April 2020</strong>¹</td>
<td><strong>Total sales revenues €129.5m in 2019; +25% vs. 2018</strong></td>
</tr>
</tbody>
</table>
| US/EU market opportunity of ~$1bn per annum  
  - Only program in clinical development  
  - Pfizer to lead late-stage development and drive commercialization | **IXIARO®**  
  - Only licensed JE vaccine for travelers in US CAN, EU; mandatory for US Military  
  - Sales > €90m in 2019 |
| **Chikungunya Phase 3 to commence Q4 2020** | **DUKORAL®**  
  - 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 | **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

2 unique late stage programs
Lyme
Chikungunya

> 500 people
Four main sites
Six in-market commercial teams

>100 people in R&D
High R&D investment in 2020 to drive Lyme and ChikV late-stage development

Inactivated SARS-CoV-2 vaccine

28 May 2020
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

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

<table>
<thead>
<tr>
<th>Virus type</th>
<th>Virus</th>
<th>Nucleocapsid</th>
<th>S</th>
<th>S1</th>
<th>S2</th>
<th>S1A</th>
<th>RBD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-coronavirus</td>
<td>SARS-CoV</td>
<td>90</td>
<td>77</td>
<td>66</td>
<td>90</td>
<td>52</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>MERS-CoV</td>
<td>49</td>
<td>33</td>
<td>24</td>
<td>43</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>HCoV-OC43</td>
<td>34</td>
<td>33</td>
<td>25</td>
<td>42</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>HCoV-HKU1</td>
<td>34</td>
<td>32</td>
<td>25</td>
<td>40</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Alphacoronavirus</td>
<td>HCoV-229E</td>
<td>28</td>
<td>30</td>
<td>24</td>
<td>35</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>HCoV-NL63</td>
<td>29</td>
<td>28</td>
<td>21</td>
<td>36</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

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

- **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


Inactivated SARS-CoV-2 vaccine
## SARS-CoV-2 vaccines
### A view on different approaches

<table>
<thead>
<tr>
<th>Inactivated vaccines</th>
<th>Nucleid acid vaccines</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Traditional technology - many licensed vaccines using this platform</td>
<td></td>
</tr>
<tr>
<td>▪ Clear regulatory path (No GMO, No foreign vector) Can be produced at high purity and large scale – significant global manufacturing capability</td>
<td></td>
</tr>
<tr>
<td>Antigen: Whole virion inactivated vaccine (Sinovac Biotech / Wuhan Institute Biol Products) (ongoing trials) / Valneva</td>
<td></td>
</tr>
<tr>
<td>Adjuvants Alum or CpG 1018</td>
<td></td>
</tr>
<tr>
<td>▪ Relatively easy and fast manufacturing process</td>
<td></td>
</tr>
<tr>
<td>▪ So far no preventive vaccines for human use on the basis of RNA or DNA has been licensed – only in clinical trials</td>
<td></td>
</tr>
<tr>
<td>Antigen: Spike protein of SARS-CoV-2</td>
<td></td>
</tr>
<tr>
<td>DNA - Electroporation needed for application (Inovio)</td>
<td></td>
</tr>
<tr>
<td>mRNA in lipid particles (Moderna), (CureVac) BioNTech use three different RNA platforms in lipid particles  - uridine RNA, modified RNA, self-amplifying</td>
<td></td>
</tr>
<tr>
<td>Antigens: Modified Spike protein SARS-CoV-2 or only the receptor bindings domain (RBD)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recombinant vaccines</th>
<th>Vector based vaccines</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Recombinant vaccines considered a well established approach and technology</td>
<td></td>
</tr>
<tr>
<td>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)</td>
<td></td>
</tr>
<tr>
<td>Adjuvanted (Matrix-M adjuvant (saponin-based) (Novavax))</td>
<td></td>
</tr>
<tr>
<td>„Molecular clamp“ technology (trimerization to enhance antigenicity) (Queensland) + Adjuvants CpG or AS0X / (GSK/ Sanofi)</td>
<td></td>
</tr>
<tr>
<td>▪ Already existing licensed vaccines (Ebola, MVA) or candidates in licensing (Adeno)</td>
<td></td>
</tr>
<tr>
<td>Antigens: Spike protein of SARS-CoV-2 or subdomains</td>
<td></td>
</tr>
<tr>
<td>Adenovirus vector - Replication-incompetent vector (E1 deleted), different types; Adenovirus type 26 vector used for Ebola vaccine (Janssen)</td>
<td></td>
</tr>
<tr>
<td>MVA vector - Replication-incompetent vector - native, full-length SARS-CoV-2 spike protein</td>
<td></td>
</tr>
<tr>
<td>Measles vector - live attenuated, replicating virus vector - native or a modified membrane-bound version of the SARS-CoV-2 spike glycoprotein</td>
<td></td>
</tr>
</tbody>
</table>
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 straightforward 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 **

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 β-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 MVSBR 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

<table>
<thead>
<tr>
<th>Molecule/Target</th>
<th>CpG 1018</th>
<th>MF59</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vaccine</strong></td>
<td>HEPLISAV-B</td>
<td>FLUAD</td>
</tr>
<tr>
<td><strong>Indication</strong></td>
<td>Hepatitis B</td>
<td>Seasonal flu</td>
</tr>
<tr>
<td><strong>Completed Clinical Trials</strong></td>
<td>10 ~14 000 patients</td>
<td>36 ~37 000 patients</td>
</tr>
<tr>
<td><strong>Sales</strong></td>
<td>35m$ (2019) Launched in 2018</td>
<td>~250m$* (2019) Not available</td>
</tr>
<tr>
<td><strong>Indications</strong></td>
<td>HIV, CRC, NHL</td>
<td>HIV, CMV, RSV, Parvo B19, GroupB Steptococcus, Pneumococcal Infections, HCV</td>
</tr>
<tr>
<td><strong>Past/Current Clinical Trials</strong></td>
<td>4 ~160 patients</td>
<td>33 ~10 000 patients</td>
</tr>
<tr>
<td><strong>Other comments</strong></td>
<td>April 2020: Dynavax and Sinovac announced Collaboration to Develop a COVID-19 inactivated vaccine</td>
<td>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.***</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Day 0</th>
<th>29</th>
<th>32</th>
<th>36</th>
<th>37</th>
<th>42</th>
<th>80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell expansion</td>
<td>Infection &amp; Harvest</td>
<td>Inactivation &amp; Purification</td>
<td>Formulation</td>
<td>Fill &amp; Finish</td>
<td>Release Testing</td>
<td></td>
</tr>
</tbody>
</table>

- 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 β-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

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Inactivated SARS-CoV-2 vaccine
Thank you.