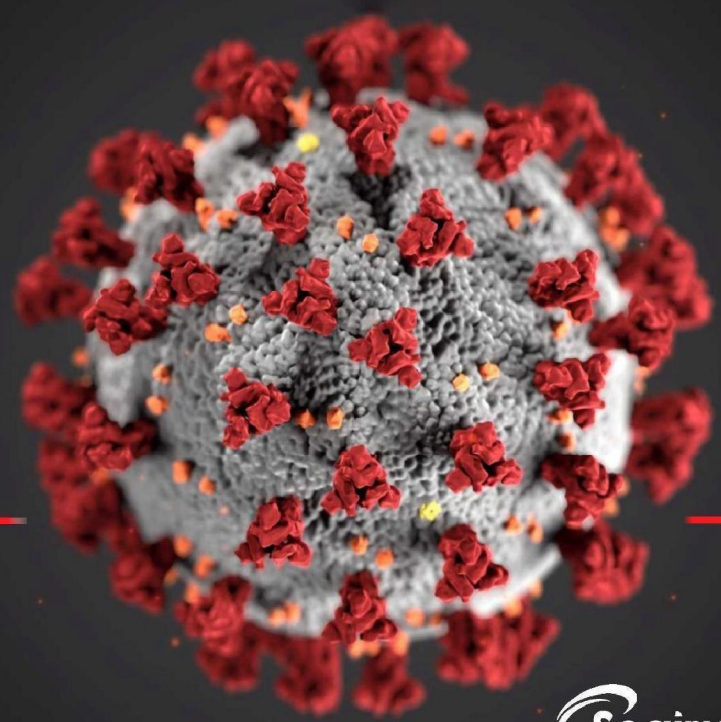
MF59-adjuvanted SARS-CoV-2 Vaccine

Presentation to National Institute for Public Health and the Environment

5.1.2e 5.1.2e

November 4, 2020



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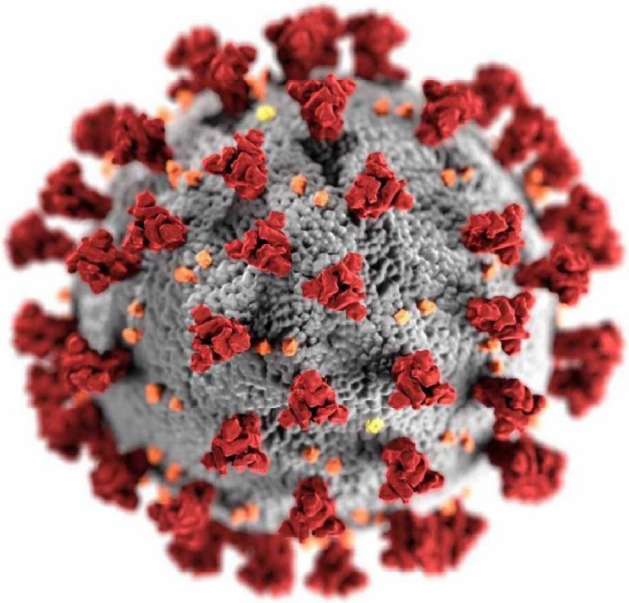

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INTRODUCTION

CSL: A LONG-STANDING HERITAGE IN PUBLIC HEALTH

- Seqirus was formed through the combination of the influenza businesses of Novartis and bioCSL
- Seqirus is part of the CSL Group, a global biotech leader in the development and large-scale manufacture of vaccines, plasma therapeutics, and recombinant proteins
- CSL was founded by the Australian Government over 100 years ago to protect against public health threats, including the 1918 Influenza pandemic
- Seqirus continues to work on the front line of influenza protection, providing innovative seasonal vaccines and pandemic preparedness solutions to public health partners around the world

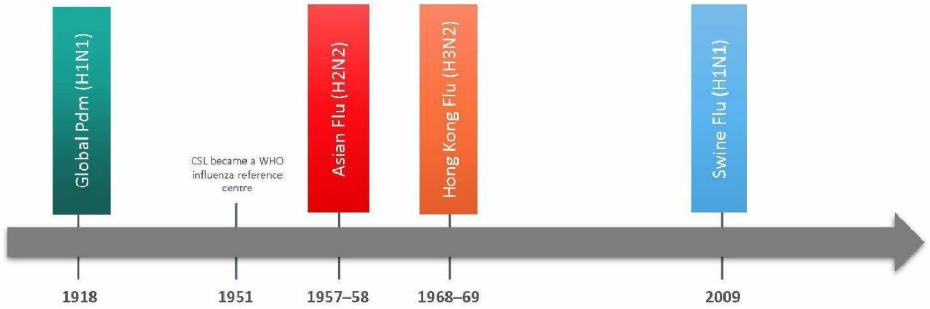

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Image: Seqirus archives.

INTRODUCTION

CSL: A GLOBAL SPECIALTY BIOTHERAPEUTICS COMPANY

DEVELOPMENT AND LARGE-SCALE MANUFACTURE OF VACCINES, PLASMA THERAPEUTICS, AND RECOMBINANT PROTEINS

60+ Countries
Of operation around the world

US$ **8.5+** Billion
In annual revenue

US$ **3.3+** Billion
In R&D investments in past 5 years advances exciting pipeline

8
Manufacturing sites

- Australia (2)
- China (1)
- Germany (1)
- Switzerland (1)
- United Kingdom (1)
- United States (1)

26,000+
Employees around the world

1700+
R&D employees

257+
Plasma collection centres across Europe and North America

Delivering **innovative** biotherapies that **save lives** and enable those with **life-threatening conditions** to live full lives

Applying **established** experience in fighting **public health emergencies** to the battle against **COVID-19**

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Source: Seqirus data on file.
COVID-19, coronavirus disease; R&D, research and development.

INTRODUCTION

CSL IS PARTNERING WITH THE UNIVERSITY OF QUEENSLAND AND CEPI TO DEVELOP A SARS-COV-2 VACCINE CANDIDATE

The University of Queensland (UQ) has initiated the development of a recombinant subunit vaccine for SARS-CoV-2 using "molecular clamp" technology

- Funding received from CEPI, the Queensland State, and Australian Federal Government to develop

CSL has entered into a partnership with UQ and Coalition for Epidemic Preparedness Innovations (CEPI) to accelerate development, manufacture, and distribution of the vaccine candidate

- UQ will lead the Phase 1 clinical study
- CSL/Seqirus will lead the later stages of clinical development, and will be responsible for regulatory submissions, process development, and manufacturing of the vaccine

CEPI and CSL/Seqirus will share the cost of the program and the doses manufactured

- CEPI's vaccine allocation will be distributed through the COVID-19 Vaccine Global Access Facility, in which CEPI works in partnership with GAVI and the World Health Organization
- CSL's allocation will supply doses to governments having entered into agreements for access
- CSL has granted CEPI a first right of refusal to any surplus doses, to be distributed through the COVID-19 Vaccine Global Access Facility

Source: CSL. The University of Queensland, CEPI and CSL partner to advance development and manufacture of COVID-19 vaccine candidate. 2020. Available at: https://www.csl.com/news/2020/20200605-uq-cepi-and-csl-partner-for-covid-19-vaccine-candidate. Accessed: July 15, 2020.
COVID-19, coronavirus disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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CSL/SEQIRUS: BRINGING CRITICAL CAPABILITIES TO THE PROGRAM

Long-standing experience in research and clinical development of innovative vaccines

Leading influenza vaccine and recombinant protein manufacturer with deep knowledge of process and formulation development and scale-up

Proven MF59® adjuvant system with 20-year history of use in influenza vaccine and unparalleled safety database

Internal manufacturing capacity to supply clinical trials and initial commercial doses

- Antigen manufacturing in CHO cells (Parkville and Broadmeadows, Australia; Marburg, Germany)
- Manufacturing of adjuvant system
- Vaccine formulation
- Filling and finishing of multi-dose vials

 CHO, Chinese hamster ovary.

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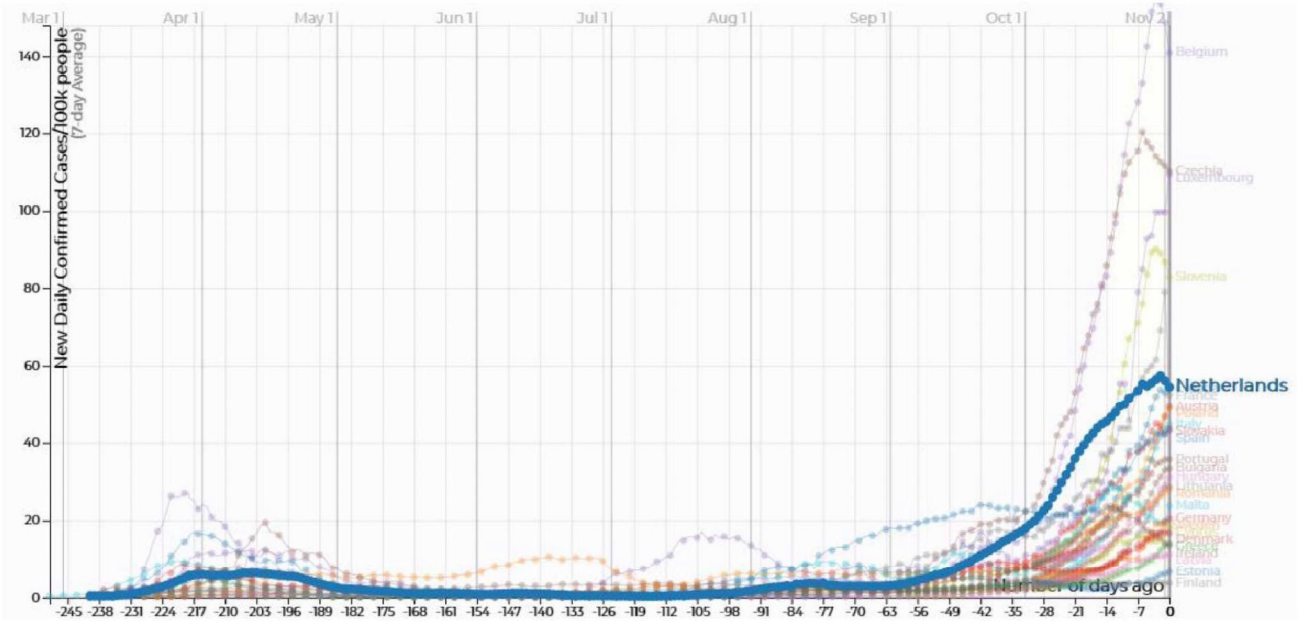
INTRODUCTION

SARS-COV2 EPIDEMIOLOGY



An interactive visualization of the exponential spread of COVID-19 | 91-DIVOC (2020). Available at: http://91-divoc.com/pages/covid-visualization/ (Accessed: 03 October 2020).

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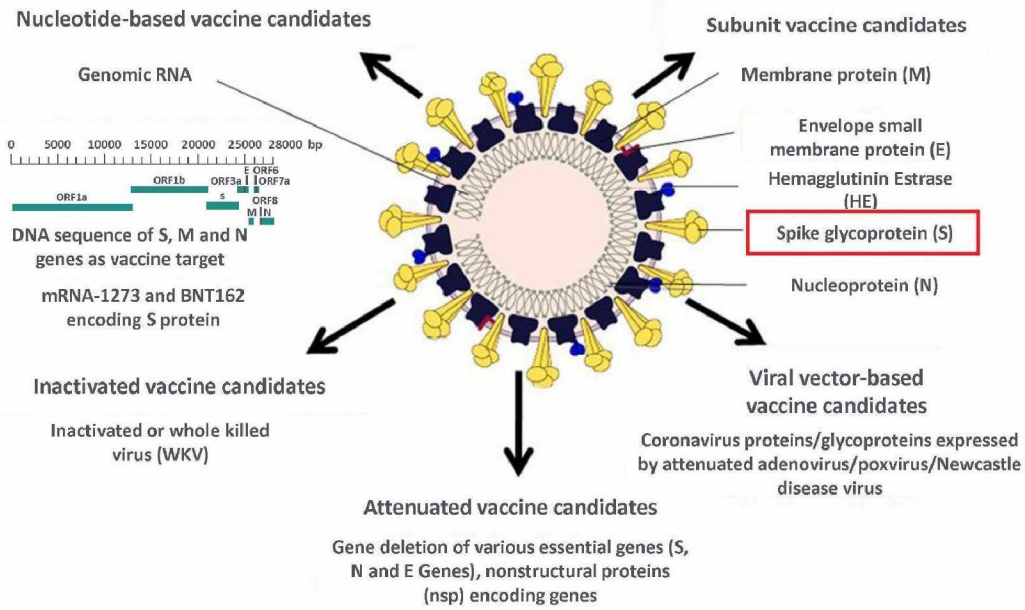
DEVELOPMENT ACTIVITIES

SARS-CoV-2: VACCINE CANDIDATES



Pandey SC et al. *Life Sciences* 2020;256:117956.
SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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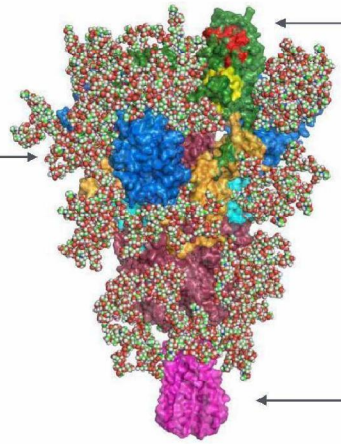
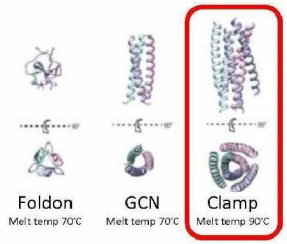
DEVELOPMENT ACTIVITIES

SARS-CoV-2: S-CLAMP ANTIGEN



Receptor binding domain
(ACE2 binding site in red)

Spike fully glycosylated with
23 N-glycans



'**clamp**' derived from **transmembrane envelope glycoprotein GP41 (HIV)**

Fully glycosylated model of SARS-CoV-2 Sclamp (MPelzing): Chimera/GlyProt

Molecular clamp aims to stabilise spike protein in trimer form

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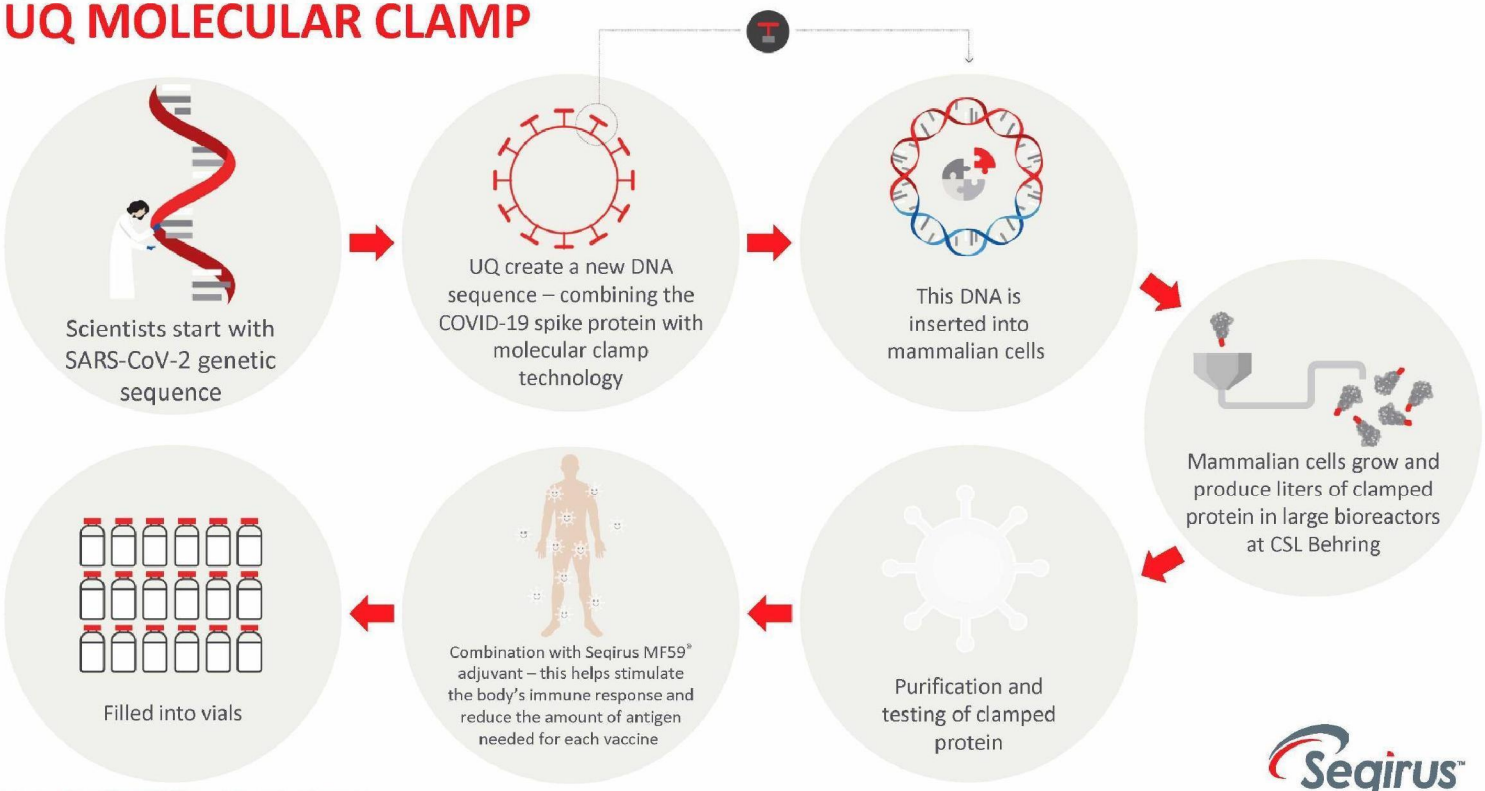
ACE, angiotensin-converting enzyme; HIV, human immunodeficiency virus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

DEVELOPMENT ACTIVITIES

UQ MOLECULAR CLAMP



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 SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; UQ, The University of Queensland.

DEVELOPMENT ACTIVITIES

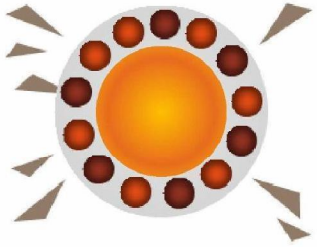
MF59®-ADJUVANTED INFLUENZA VACCINES DEMONSTRATED FAVORABLE EFFICACY AND SAFETY PROFILES IN ALL POPULATIONS

Antigen Sparing

- H5N1 and H1N1 clinical trials showed 1/4 to 1/12 of antigen sufficient to meet approval criteria compared with unadjuvanted vaccines†,[1–3]

Safety Profile

- 20 years of seasonal, pandemic, and pre-pandemic use[1,2]
- >150 million doses distributed[1,2,10]
- Data from more than 100,000 subjects in clinical and observational trials[11]
- Controlled trial data in >5000 children, 18,000 adults, and 15,000 elderly[11]
- No safety signals in clinical trials or pharmacovigilance databases[11]



Cross Protection

- MF59® expands antibody repertoire[4]
- Primed subjects generate cross-reactive antibodies[5,6]

Higher Immunogenicity

- MF59®-primed subjects have higher antibody responses[7,8]
- In an animal model MF59®-adjuvanted vaccine lead to absence of H1N1 in lungs and nose[9]

†Unadjuvanted H5N1 vaccine requires 90 µg HA.

[1]Keitel W et al. *Vaccine*. 2010;28:840–848; [2]Vesikari T et al. *Vaccine*. 2012;30:1388–1396; [3]Frey S et al. *Vaccine*. 2003;21:4234–4237; [4]Seqirus, pharmacovigilance data on file; [5]Podda A, Del Giudice G. *Exp Rev Vaccines*. 2003;2:197–204; [6]O'Hagan DT. *Exp Rev Vaccines*. 2007;6:699–710; [7]Galli G et al. *Proc Natl Acad Sci USA*. 2009;106:7962–7967; [8]Del Giudice G et al. *Sci Transl Med*. 2009;1:12re1; [9]Khurna S et al. *Sci Transl Med*. 2010;2:15ra5; [10]Black S. *Vaccine*. 2015;33:B3–5; [11]Panatto D. et al *Influenza Other Respir Viruses*. 2020;14:61–66.

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DEVELOPMENT ACTIVITIES

COVID-19 VACCINE: DEVELOPMENT

- COVID-19 vaccine is a recombinant subunit vaccine manufactured using a stably transfected CHO cell line
- COVID-19 vaccine is highly purified and well characterized
- MF59® adjuvant has a comprehensive safety profile
- Medicinal products developed by biotechnological processes, such as recombinant DNA technology, fall within the mandatory scope of the Annex of Regulation (EC) No 726/2004. Applicants are obliged to use the EMA centralized procedure

 CHO, Chinese hamster ovary; COVID-19, coronavirus disease; DNA, deoxyribonucleic acid; EMA, European Medicines Agency.

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DEVELOPMENT ACTIVITIES

KEY ELEMENTS OF THE PRODUCT PROFILE TO BE CONFIRMED BY DEVELOPMENT ACTIVITIES

Indication:	For active immunization of at-risk persons to prevent COVID-19 illness
Initial target population:	Adults, including elderly
Special populations:	Individuals with chronic medical conditions
Efficacy:	Meeting approval criteria for efficacy
Safety:	Safety and reactogenicity supporting a highly favorable benefit/risk profile
Dosage form:	10 to 20 dose vial; ready to use
Dose regimen:	2 doses of 0.5 ml given approximately 3 to 4 weeks apart
Route of administration:	IM injection into deltoid muscle
Storage conditions:	Refrigerated (2-8°C) and protected from light; not to be frozen
Stability:	6 to 12 months

CHO, Chinese hamster ovary; COVID-19, coronavirus disease; DNA, deoxyribonucleic acid; EMA, European Medicines Agency.

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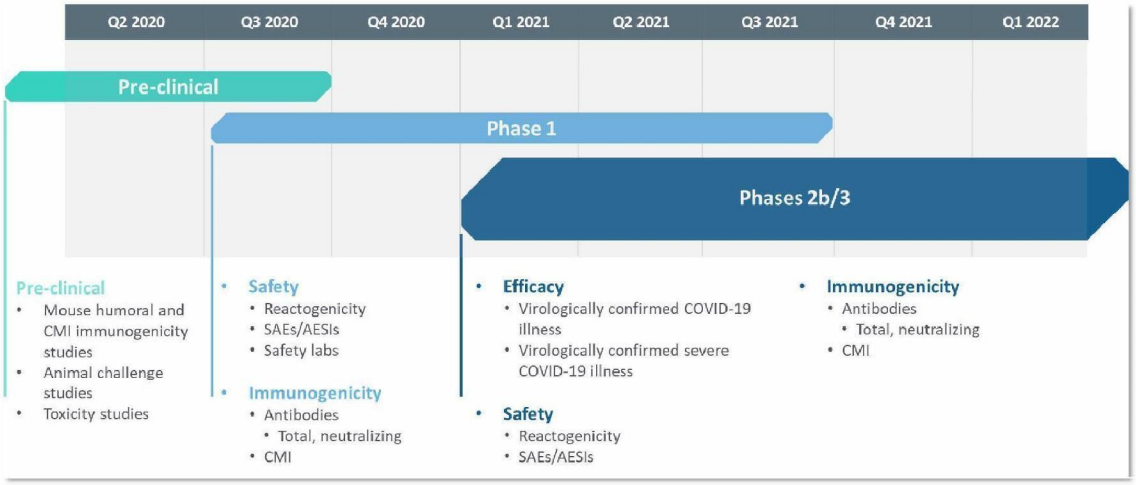
DEVELOPMENT ACTIVITIES

ACCELERATED TIMELINE
PHASE 3 STUDY STARTS DECEMBER 2020



Ph1b >55y

Ph 3 with Ph2 lead-in N=28,000

Interim analysis date depends on attack rate and vaccine efficacy

AESI, adverse event of special interest; CMI, cell-mediated immunity; COVID-19, coronavirus disease; Q, quarter; SAE, serious adverse event.

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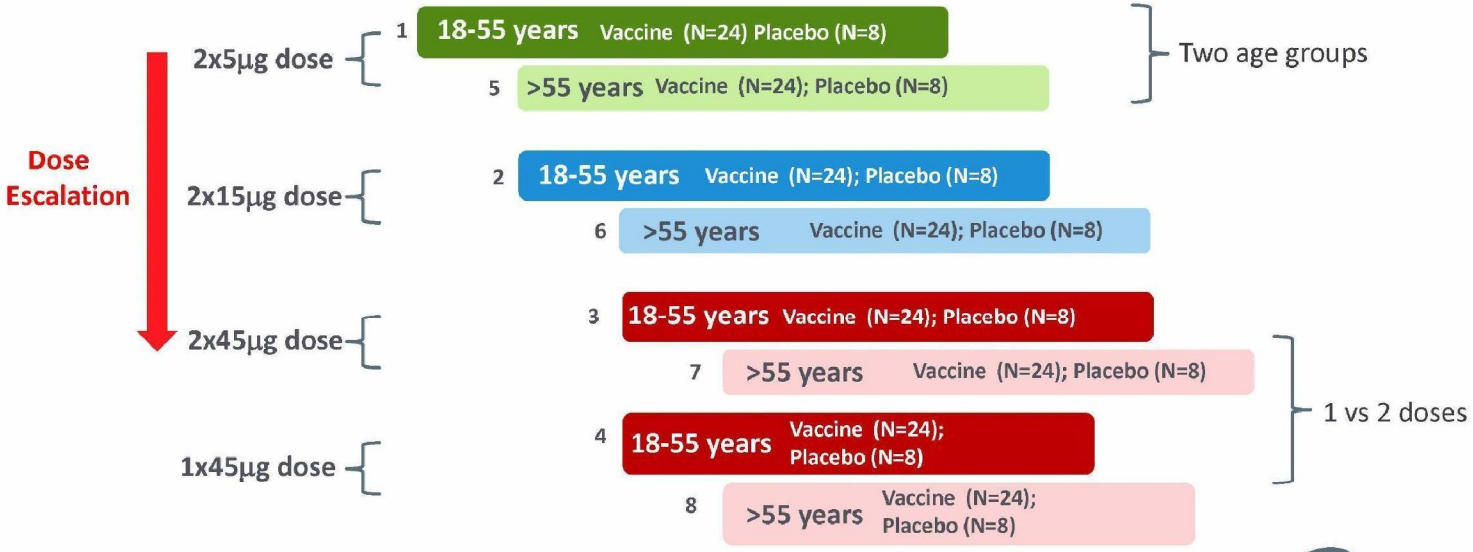
DEVELOPMENT ACTIVITIES

PHASE 1/1B STUDY DESIGN ELEMENTS



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DEVELOPMENT ACTIVITIES

PHASE 1/1B STUDY OBJECTIVES AND PROCEDURES

Primary Safety Objective:
Safety and reactogenicity of aCoV2 in adults/older adults

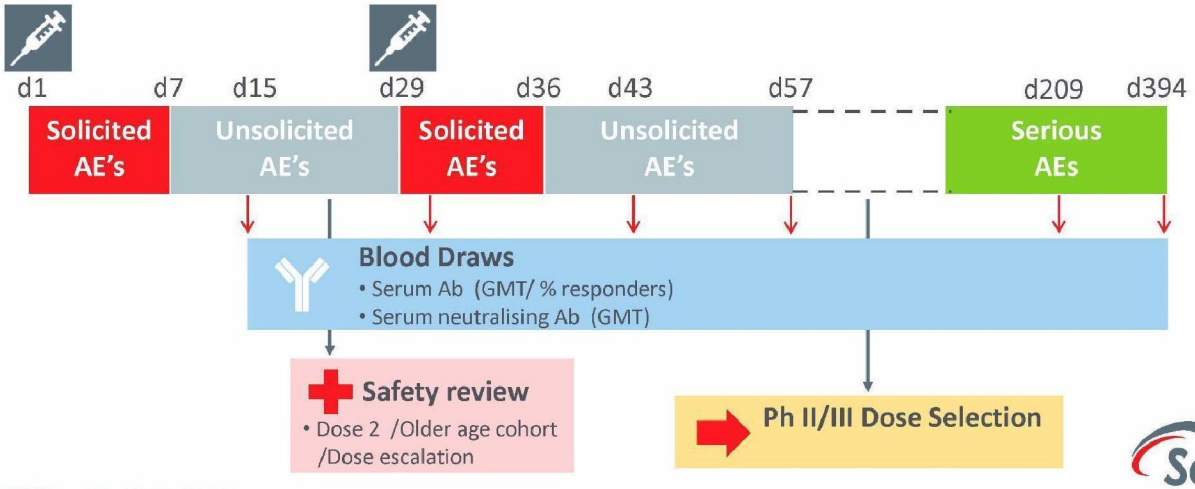
Primary Immunogenicity Objective:
Humoral responses (NAb and total Ab) to aCoV2 in adults/older adults (D29, D57)

Secondary Immunogenicity Objectives:

1. Persistence of humoral responses (6- and 12-mth)
2. Cell-mediated immune responses (up to D57)

Exploratory Objective:

Evaluate frequency and severity of SARS-CoV-2 infections



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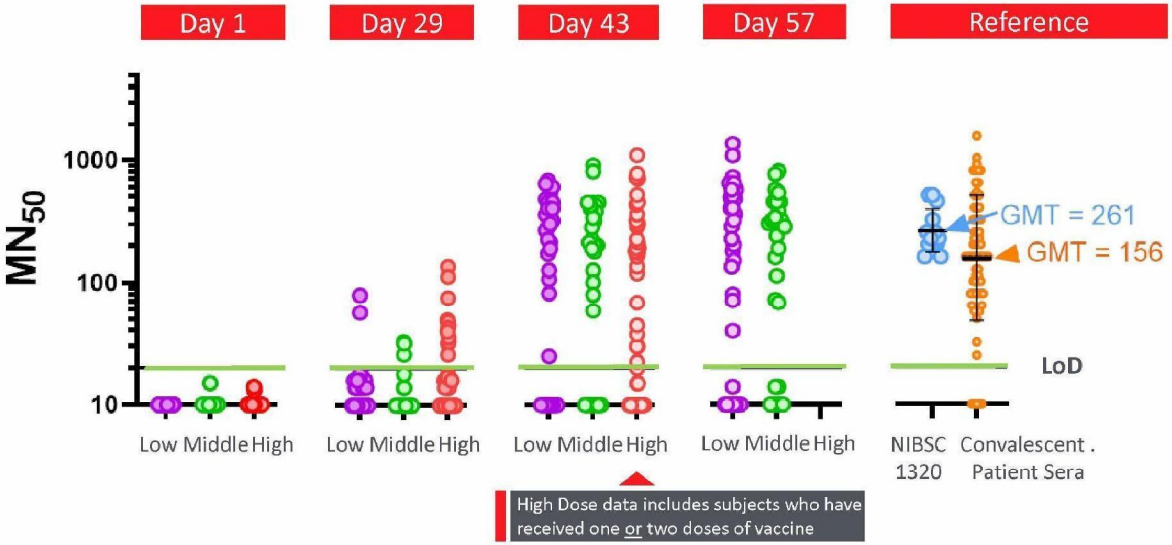
PHASE 1 DATA UPDATE

PHASE 1 ANTIBODY RESPONSES

MICRONEUTRALISATION ASSAY RESULT; AVERAGE OF 2-4 ASSAYS PER SAMPLE



 BLINDED DATA INCLUDES ACTIVE AND PLACEBO ARMS; High dose Day 57 and older cohorts to come

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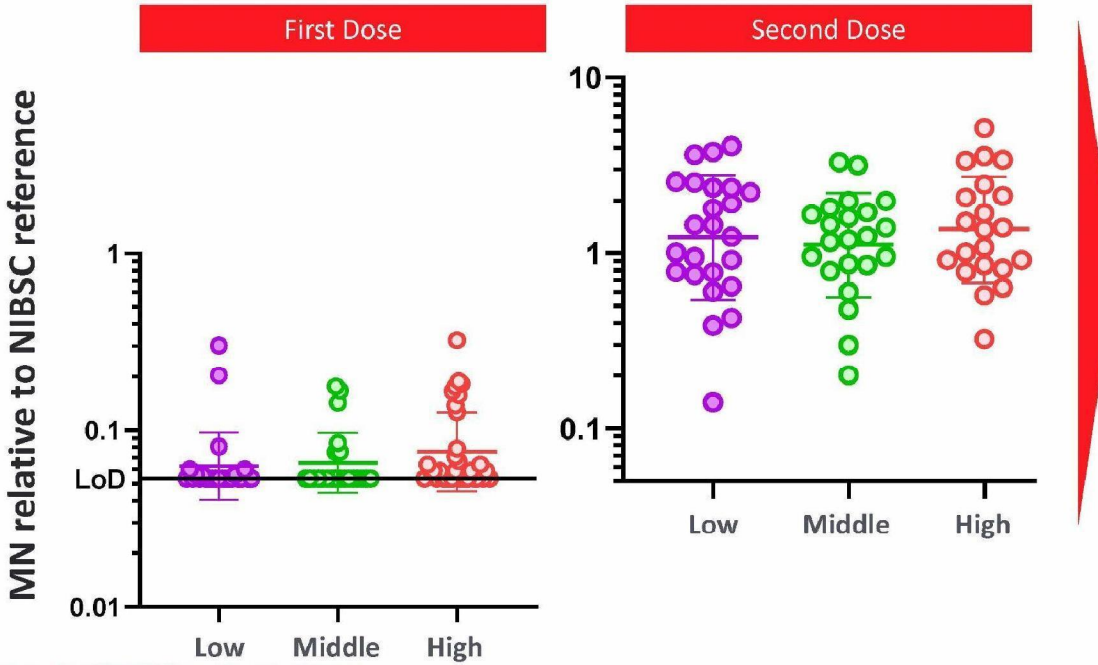
PHASE 1 DATA UPDATE

MICRONEUTRALISATION RESULT

NORMALISED FOR INTER EXPERIMENTAL VARIATION BASED ON NIBSC REFERENCE SERUM



Number of top responders equivalent to active regiment included

No difference in microneutralisation assay result for 5 µg, 15 µg or 45 µg after one or two doses

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PHASE 1 DATA UPDATE

PRELIMINARY SAFETY RESULTS
BLINDED DAY 15 DATA

- Three cohorts presented
- Subjects aged 18 - 55 years
  - Cohort 1: two doses, 5µg
    - N = 32
  - Cohort 2: two doses, 15µg
    - N = 32 (29 for dose 2)
  - Cohort 3: two doses, 45µg
    - N = 56 (52 for dose 2)

- Safety summary
  - Two SAEs reported, not assessed as related (not present in data listings)
  - Most commonly reported solicited AEs
    - Local: Pain, tenderness
    - Systemic: Headache, fatigue, malaise, myalgia
  - Unsolicited AEs reported most frequently in Cohort 1 (due to more complete follow up)
    - Related unsolicited AEs reported at similar frequency in the three cohorts

Data reviewed by independent Safety Review Committee.

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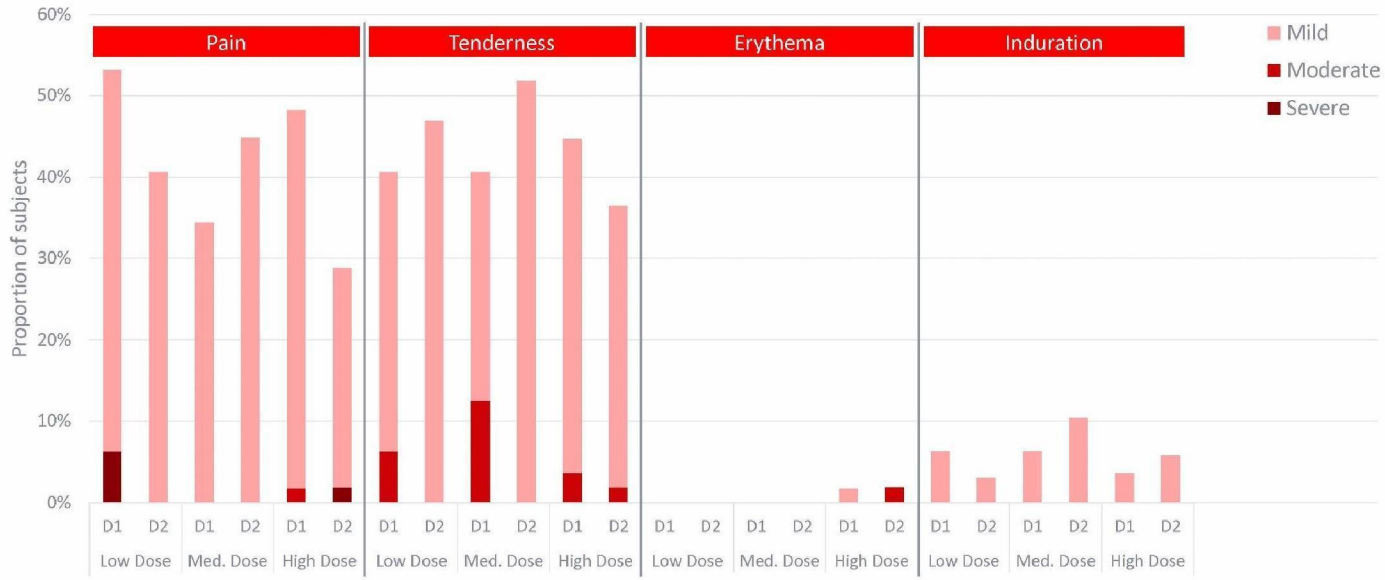
PHASE 1 DATA UPDATE

SOLICITED LOCAL ADVERSE EVENTS

ADULTS 18-55 YRS; 5, 15 & 45UG; BLINDED DAY 15 DATA



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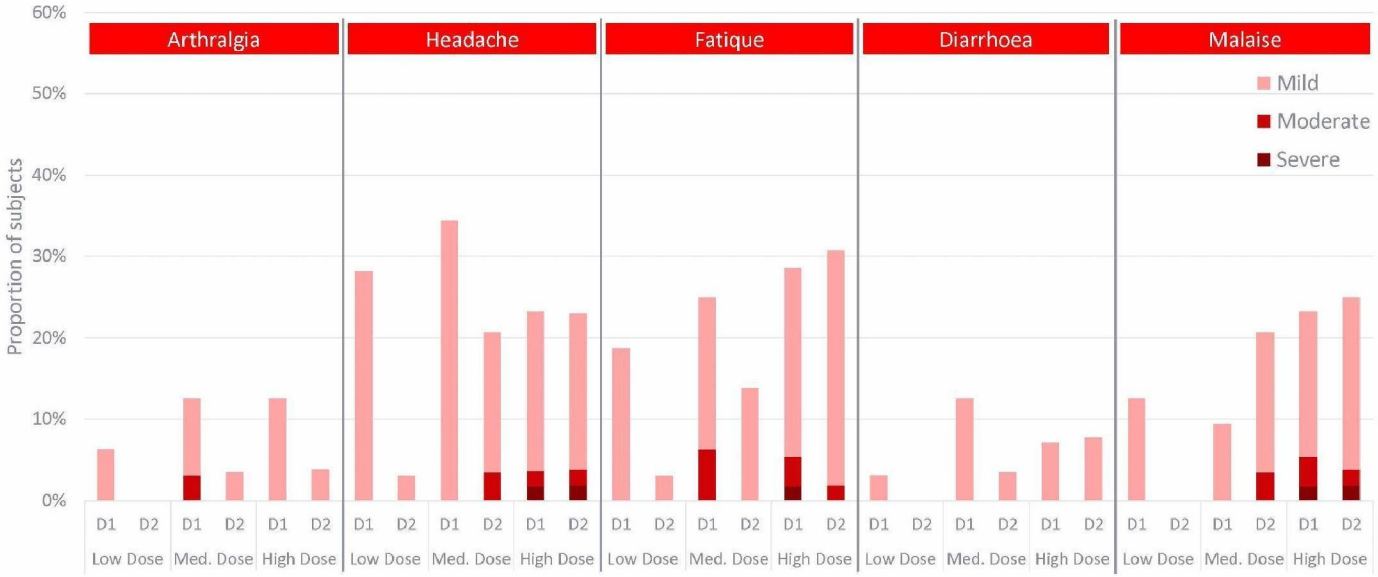
PHASE 1 DATA UPDATE

SOLICITED SYSTEMIC ADVERSE EVENTS 1

ADULTS 18-55 YRS; 5, 15 & 45UG; BLINDED DAY 15 DATA



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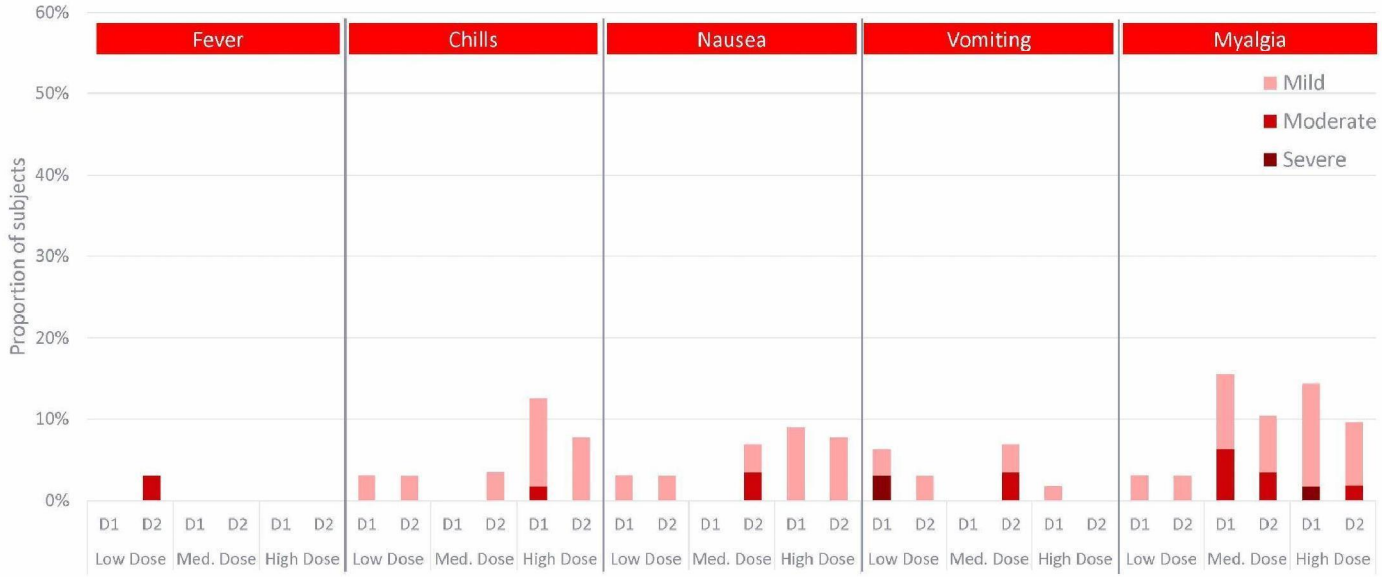
PHASE 1 DATA UPDATE

SOLICITED SYSTEMIC ADVERSE EVENTS 2

ADULTS 18-55 YRS; 5, 15 & 45UG; BLINDED DAY 15 DATA



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PHASE 1 DATA UPDATE

UNSOLICITED ADVERSE EVENTS

ADULTS 18-55 YRS; 5, 15 & 45UG; BLINDED DAY 15 DATA

Cohort	N	Unsolicited AEs		Related unsolicited AEs*	
		n events / subjects	%	n events / subjects	%
Cohort 1 Low Dose (5 µg)	32	22 / 15	46.9	8 / 7	21.9
Cohort 2 Middle Dose (15 µg)	32	15 / 11	34.4	5 / 5	15.6
Cohort 3 High Dose (45 µg)	56	24 / 15	26.8	10 / 8	14.3

*Causality assessment not provided for all events

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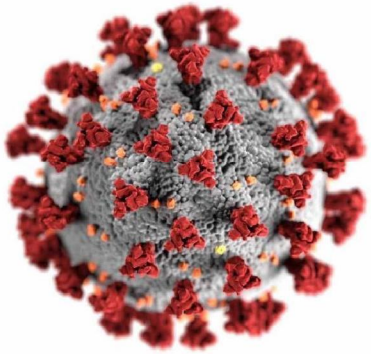
MOLECULAR CLAMP ANTIBODIES

PRECLINICAL DATA: NO INTERACTION WITH NEUTRALIZATION

PHASE 1 DATA: INTERACTIONS WITH HIV DIAGNOSTIC ASSAYS



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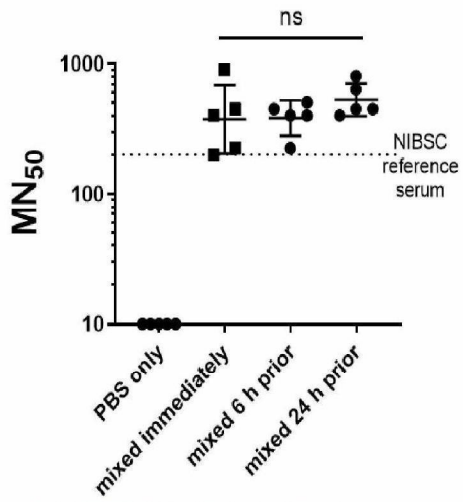
PHASE 1 DATA UPDATE

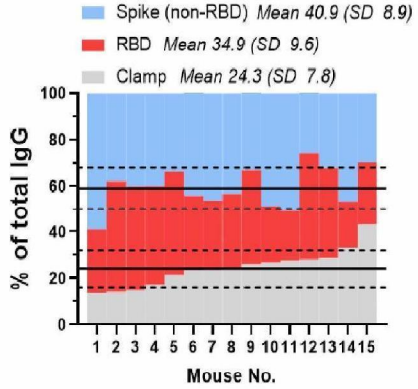
ANTIBODY RESPONSES TO RECEPTOR BINDING DOMAIN AND CLAMP

PRECLINICAL DATA MOUSE

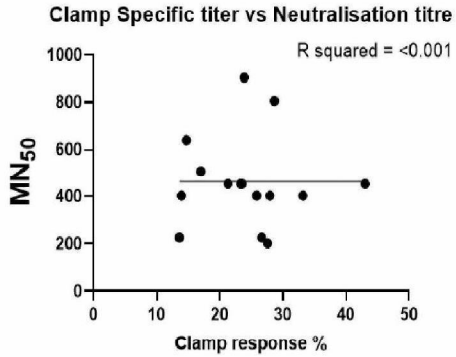
Neutralisation comparable to convalescent serum



Ab to Spike dominates



No relationship between clamp Ab and neutralisation



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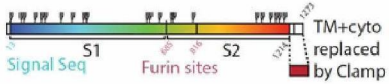
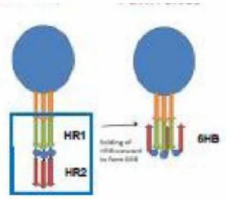
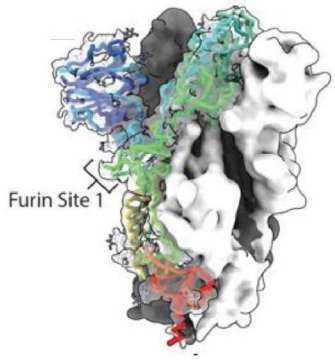
PHASE 1 DATA UPDATE

PHASE 1 DATA - MOLECULAR CLAMP ANTIBODIES & HIV ASSAYS

- Molecular Clamp of adjuvanted SARS-CoV2 vaccine is trimerization domain composed of the HR1 & HR2 regions of HIV gp41
- Known potential risk of impact of molecular clamp antibodies on HIV assays included in Ph 1 study consents
- UQ investigators tested blood @8w for 29 study participants on medium dose (22 had 15µg dose, 7 placebo) using range of HIV assays







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PHASE 1 DATA UPDATE

DIAGNOSTIC INTERFERENCE WITH CERTAIN HIV ASSAYS

Interference observed with certain HIV assays

- Point-of-care assays
  On 2/4 assays, 22/29 participants had false positive/indeterminate results
- Self test (1/1 assays), and
- Lab-based assays (2/3 assays)

Nucleic acid testing not affected (29/29 participants)

Not all tests recorded reactive or indeterminate results; further investigations are underway.

- Assays that use gp41 peptides rather than whole glycoprotein appear not to be affected

Unlikely to have any direct safety impact on study participants

Evaluating persistence of antibodies and additional appropriate assays for use

Test	Format	Result
Alere/ Abbott - Determine HIV-1/2 - test gp41 recombinant	Point of care	Reactive
Uni Gold HIV Test gp41 recombinant	Point of care	Reactive
Atomo HIV Self-Test	Self Test	Reactive
OraQuick Advance HIV-1/2 (Integrated Sciences) (gp-41 peptide).	Point of care	Non reactive
Bio-Rad Genius HIV 1/2 Assay (gp-41 peptide).	Point of care	Non reactive
Bio-Rad Genscreen HIV 1/2 Ab-Ag ELISA (gp-41 peptide).	Lab	Non reactive
ARCHITECT(®) HIV Ag/Ab Combo Assay gp41 recombinant	Lab	Reactive
DiaSorin Liaison HIV 1/2 Ab-Ag gp41 recombinant	Lab	Reactive
Western Blot Assay –confirmatory assay for immunoassay	Lab	Indeterminate in 20/22 tested, reactive in 2/22
Nucleic Acid Testing (Roche COBAS)	Lab	Not detected

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PHASE 1 DATA UPDATE

PREVIOUS REPORTS OF DIAGNOSTIC INTERFERENCE WITH HIV ASSAYS

- Known biological false positives: frequent blood transfusion, pregnancy, autoimmune diseases, vaccination[1]
- Case report of two patients with SARS-CoV-2 natural infection having reactive HIV assay on Architect machine. No interference on other assays tested[2].
- Previous report that suggested gp41 partly acts like S2 of SARS-CoV-1 with similarity in conformation motif[3]
- Pandemrix pandemic adjuvanted vaccine label reports transient false positive on some HIV assays after vaccine[4]
- gp120 HIV vaccine study participants had alternative diagnostic testing algorithms developed[5]

1 Public Health Laboratory Network HIV Laboratory Case Definition www1.health.gov.au/internet/main/publishing.nsf/Content/cda-phlncd-HIV.htm
2 Clin Pathol 2020;0:1.
3 BMC Microbiology 2003,3:20
4 AUSPAR Pandemrix accessed from TGA website 20/10/20
5 Personal communication S Lewin

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PHASE 1 DATA UPDATE

PLANNED ACTIVITIES

- **Further Data**
  - Changes over time in assay results; results against assays used in full range algorithms around world
  - Ph2 study in people living with HIV
- **Implications for HIV diagnostic algorithms**
  - Exploration modification algorithms
  - Working with HIV experts (Doherty/Kirby) and Pathology providers to explore HIV assay algorithms to avoid false positive test results and to differentiate if indeterminate
- **Communication and Education**
  - Government(s) stakeholders
  - Regulators
  - CEPI
  - HCPs likely to test for HIV: Communication in label and through medical education
  - Potential recipients of vaccine: general public (through HCP)

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DEVELOPMENT ACTIVITIES

PHASE 2/3 STUDY DESIGN ELEMENTS AND OBJECTIVES (V451_07)

Study Design

- Pivotal Ph2/3 Efficacy, Immunogenicity and Safety
- Event driven study. 1:1 ratio. **N=28,600 subjects**
- Adults 18–55 years and 56 yrs+, up to 20% 70yrs+
- Dose selected from Ph1/1b: 2-doses, 28 days apart
- 600 subject 'lead-in' for safety review prior to further enrolment for demonstration for efficacy
- All subjects included in efficacy follow-up
- *HIV testing – baseline and EoS*

Statistical Assumptions

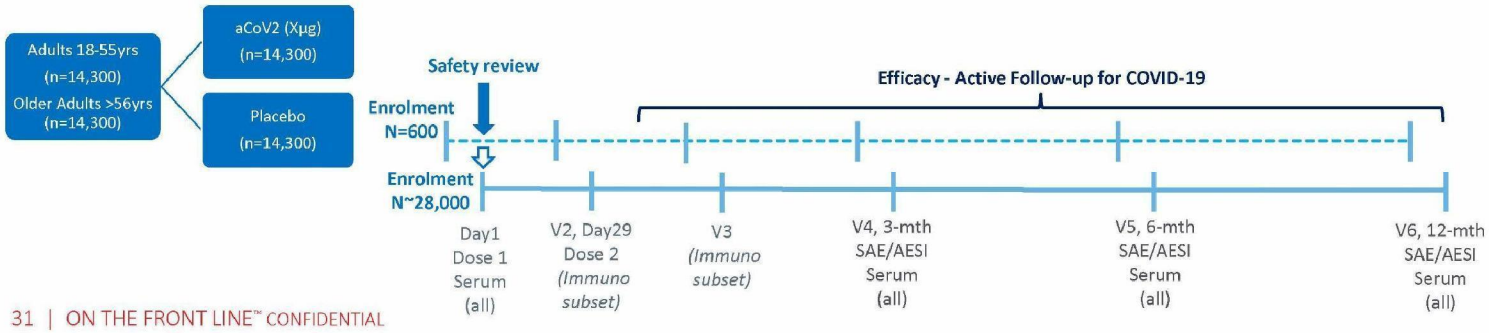
- VE ≥60%; LL ≥30%; Cases =151 (aCoV2 =43: placebo =108)
- Power 93%; α=0.025; attack rate 0.8%

Primary Objective: Efficacy of aCoV2 to prevent the first occurence of virologically-confirmed symptomatic COVID-19 (ECDC definition: LL ≥20%)

Co-Primary Objective: Efficacy of aCoV2 to prevent the first occurence of virologically-confirmed symptomatic COVID-19 (FDA definition: LL ≥30%)

Secondary Objectives:

1. Efficacy of aCoV2 to prevent virologically-confirmed severe COVID-19 disease
2. Efficacy of aCoV2 to prevent hospitalization due to virologically-confirmed COVID-19
3. Efficacy of aCoV2 to prevent ICU admission due to virologically-confirmed COVID-19
4. Efficacy of aCoV2 to prevent all-cause mortality in COVID-19 confirmed subjects
5. Humoral responses (NAb and Spike Ab) to aCoV2 (V2, V3, V4, V5, and V6)
6. Cell-mediated immune responses to aCoV2 in adults/older adults (up to V3)
7. Safety and reactogenicity of aCoV2, including SAEs/AESIs
8. Efficacy of aCoV2 to prevent SARS-CoV-2 infection (regardless of symptomology)



VACCINE ACCESS

STAGED PAYMENTS BASED UPON DEVELOPMENT SUCCESS

A risk-sharing approach to payment:

- A vaccine in development must pass a number of critical "stage gates" to get to the next stage of development – usually related to clinical success or manufacturing scale-up
- Later stages of development – Phase 3 trials and industrial scale-up – are the most expensive
- Seqirus proposes a number of staged payments, coinciding with stage-gate successes
- The proportion of the final cost payable at each stage will be equivalent to the proportion of the overall development investment made by Seqirus

Seqirus™
A CSL COMPANY