Safety & Immunogenicity of a Plant-Derived Coronavirus-Like Particle Vaccine Candidate with GSK's Pandemic Adjuvant in Adults Aged 18-55

EU Member States Update

Preprint link: https://doi.org/10.1101/2020.11.04.20226282

December 2020

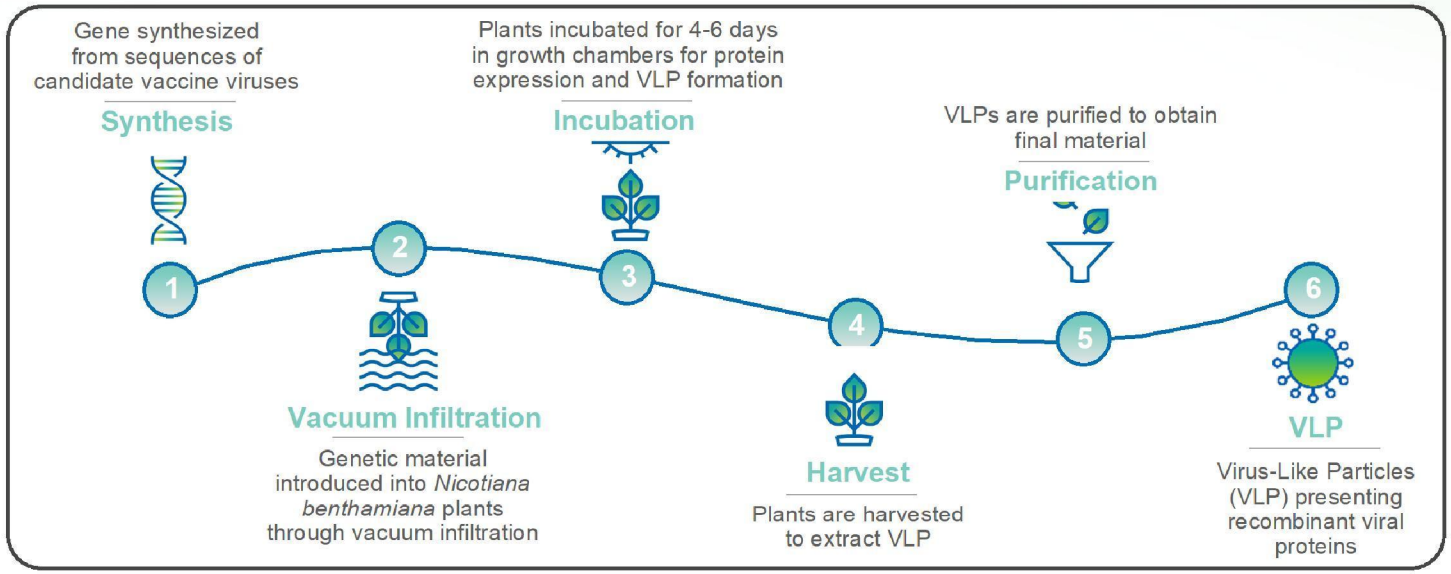
AGENDA

- **Medicago and its technologies**
- CoVLP preclinical results
- CoVLP Phase 1 results
- Next steps, CoVLP Development Program

Medicago at a glance

- Canadian biopharma with the mission to create and rapidly deliver effective responses to emerging global health challenges
- Focus on plant-derived vaccines & therapeutic proteins with 2 lead vaccine candidates: COVID-19 and influenza
- Extensive development experience with 17 clinical trials and more than 27,000 subjects enrolled
- Our team includes over 450 scientific experts and employees in Canada and the United States
- Manufacturing footprint in US & Canada

Discover Proficia®, our plant-based vaccine technology



Discover our plant-based technology: https://youtu.be/wH3-b58MFCw

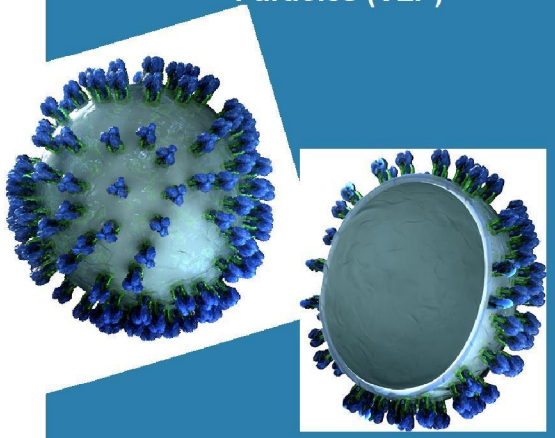
Advantages of Medicago's Platform For COVID-19 Pandemic Response

Protein-based antigens	• Vaccines from similar protein-based antigens technologies already on market • Medicago's quadrivalent influenza vaccine under registration in Canada and its peer-reviewed, phase 3 results, have been published in The Lancet*
Safety profile	• Strong safety database of more than 14,500 subjects built over 17 human clinical trials
Manufacturing experience	• COVID-19 vaccine processes based on seasonal flu processes • US & Canada based / Tech transfers experience • Previous success with DARPA in 2012: production of 10M influenza pandemic doses within 1 month
Easy distribution	• Standard cold chain requirements (2-8C)

* Available at https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32010-9/fulltext

Medicago's Plant-Derived Virus-Like Particles (VLP)

Plant-derived Virus-Like Particles (VLP)



- Complex product composed of recombinant protein embedded in plant lipid bilayer
- Electron microscopy shows VLP similar in size to virus and presenting recombinant protein on its surface similarly to a real virus (e.g., trimers for HA influenza)
- No live virus → No infectious content and no chemical viral inactivation required
- No safety issues observed with plant lipids / glycosylation
- VLPs have been in use for over 30 years in other vaccines such as Hepatitis B and HPV

Medicago's Clinical Vaccine Development Programs

Disease	Phase	Candidate vaccine	Subjects enrolled	Year
Pandemic influenza	Phase 1	• H5 VLP + Alhydrogel® • H1 VLP • H5 VLP + GLA (IDRI) ID • H7 VLP + Alhydrogel®	• 48 healthy adults (18-60 y) • 100 healthy adults (18-49 y) • 100 healthy adults (18-49 y) • 100 healthy adults (18-60 y)	• 2009 • 2011 • 2013 • 2014
	Phase 2	• H5 VLP + Alhydrogel® • H5 VLP + GLA or Alhydrogel®	• 255 healthy adults (18-60 y) • 390 healthy adults (18-60 y)	• 2010 • 2014
Seasonal influenza	Phase 1/2	• Quadrivalent VLP	• 120 healthy adults (18-49 y)	• 2014
	Phase 2		• 300 healthy adults (18-49 y) • 450 subjects (≥50 y) • 900 healthy adults (18-64 y) • 1000 subjects (≥50 y) • 100 subjects (18-49 & ≥65 y)[1]	• 2015 • 2015 • 2016 • 2016 • 2018
	Phase 3		• 10,000 subjects (18-64 y)[2*] • 1200 healthy adults (18-49 y)[3] • 12,000 subjects (≥65 y)[2*]	• 2017 • 2017 • 2018
Rotavirus	Phase 1	• MT-5625 (Mitsubishi Tanabe Pharma)	• 110 adults, toddlers & infants	• 2018
COVID-19	Phase 1	• CoVLP, Adjuvanted CoVLP	• 180 healthy adults (18-55 y)	• 2020

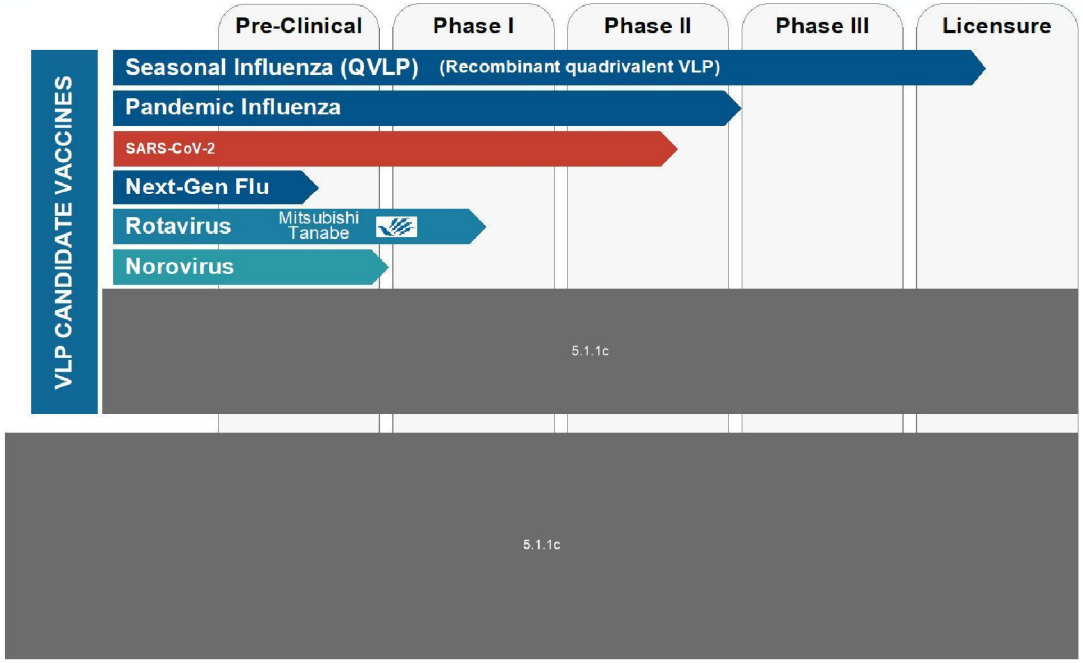
17 clinical trials
> 27,000 subjects enrolled

> 10 years clinical experience

1. Extended immunogenicity
2. Efficacy study
3. Lot to lot study

* Efficacy study results in 18+ published in The Lancet. 2020 Oct 13:S0140-6736(20)32014-6. doi: 10.1016/S0140-6736(20)32014-6.

MEDICAGO PRODUCT PIPELINE



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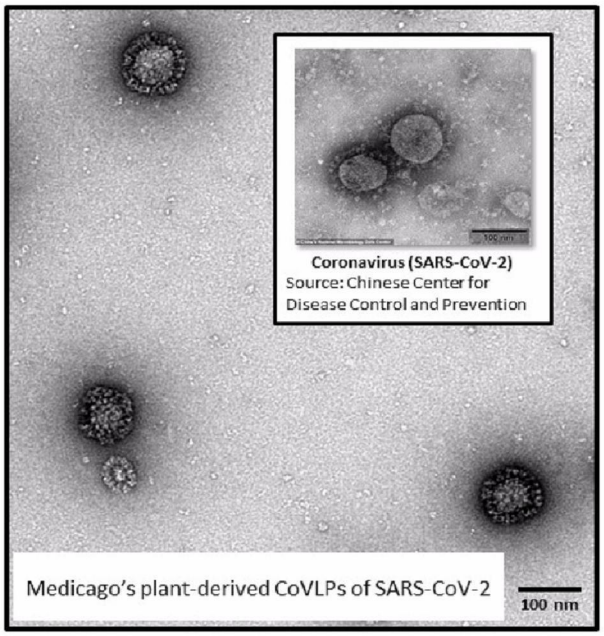
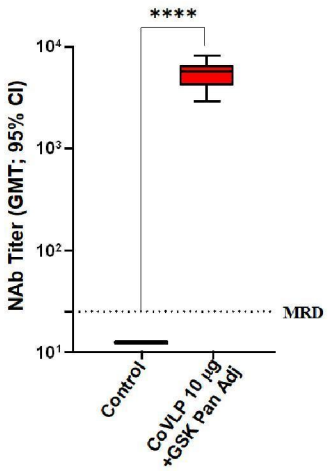
Medicago's Plant-Derived Virus-Like Particles (VLP)



- Complex product composed of recombinant protein embedded in plant lipid bilayer without genetic material
- Electron microscopy shows VLP similar in size to virus and presenting recombinant protein on its surface similarly to a real virus (eg: SARS-CoV-2 Spike protein)
- Standard cold chain requirements (2-8°C)

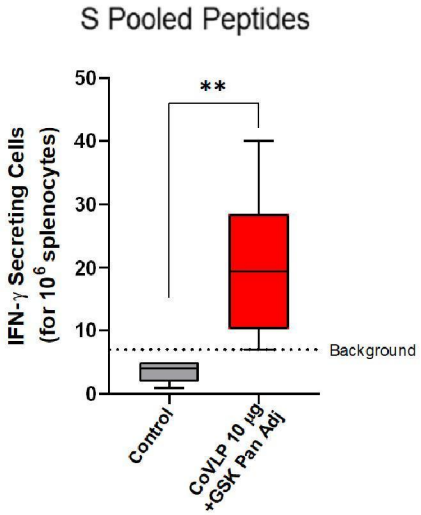
Humoral and Cell-Mediated Immune Responses in Mice 14 Days Post-1 Boost with 10 µg CoVLP Vaccine Candidate + GSK's Pandemic Adjuvant

Neutralizing Antibodies



Neutralizing antibody (NAb) titers were measured in serum samples 14 days after the boost (study day 35) using a cell-based pseudovirus neutralization assay. Results are presented as geometric mean of NAb titers (GMT) with 95% confidence interval (CI). Half of the minimum required dilution (MRD) of the method was assigned to non-responders (i.e 50 for IgG titers and 12.5 for NAb Titers) for GMT calculation purposes.. ****p < 0.0001. Statistical comparisons were performed using One-way ANOVA

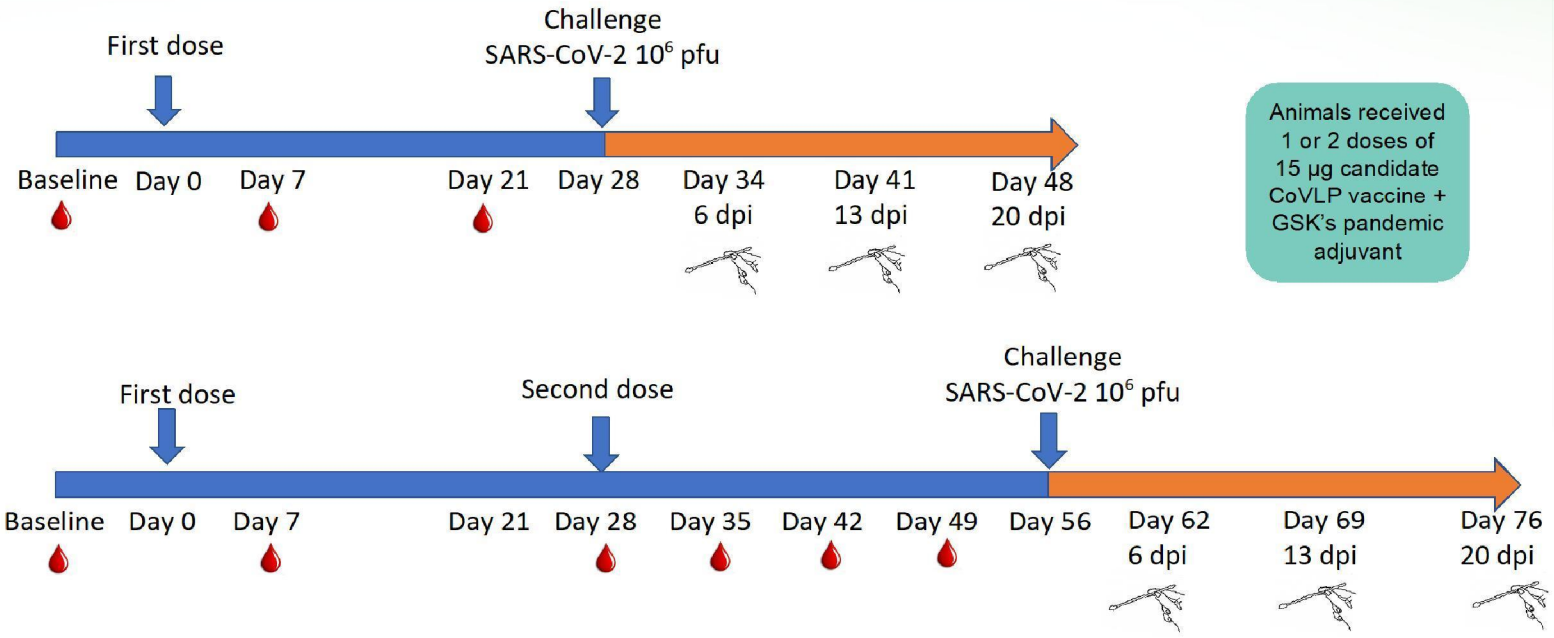
IFN-γ Secreting Cells



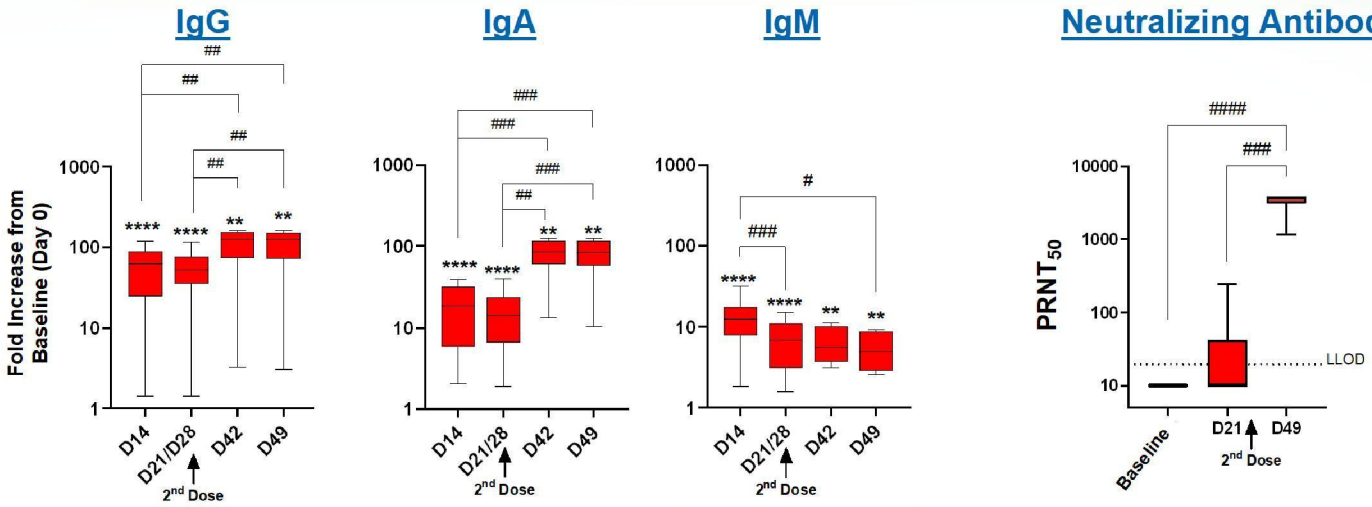
Results obtained by ELISpot; median and interquartile range are represented. Statistical significance was assessed using a non-parametric Kruskal-Wallis test. P-Value < 0.05 was considered significant. **p < 0.01. Background represents the mean of the unstimulated results obtained for all the samples.

CoVLP vaccine candidate + GSK's pandemic adjuvant induced neutralizing antibodies and cell-mediated immune response in mice

Sampling Timeline of Preclinical Studies in Macaques with 15 µg CoVLP Vaccine Candidate + GSK's Pandemic Adjuvant



Humoral Response in Macaques after One and Two 15 µg-Doses of CoVLP Vaccine Candidate + GSK's Pandemic Adjuvant

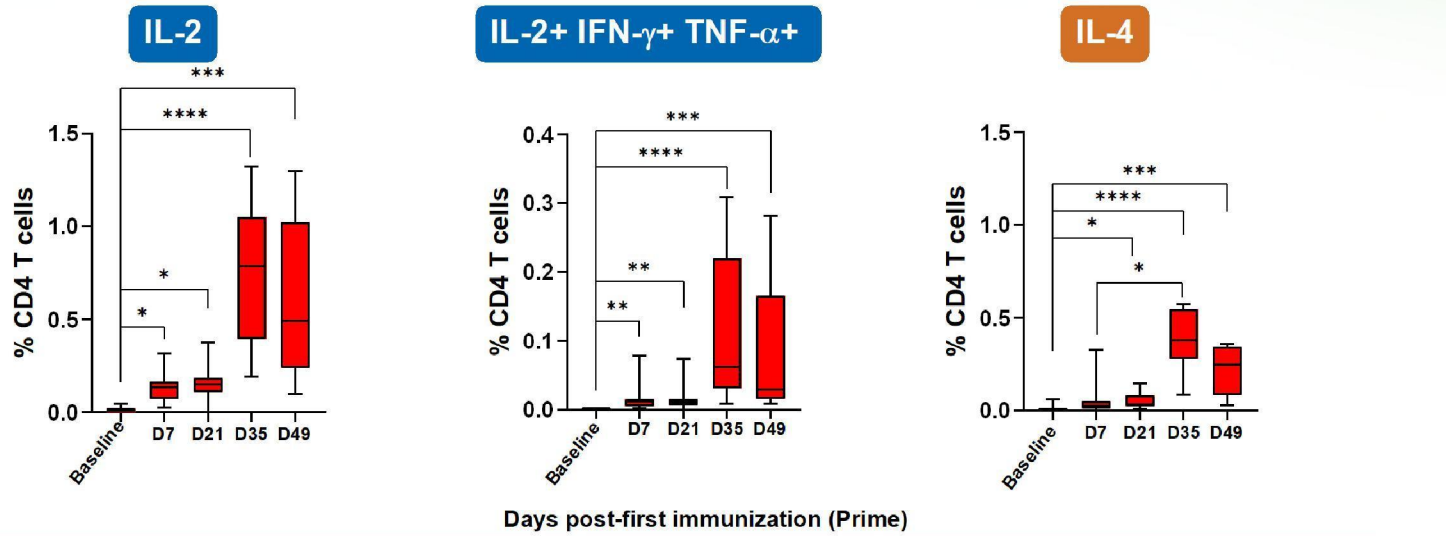


Medicago Inc. Data on file. Fold increase from baseline (Day 0) of anti RBD IgG, IgA and IgM in serum of macaques after IM immunization with one and two dose(s) of 15 µg CoVLP 28 days apart with GSK's pandemic adjuvant. Median (line), 25th/75th percentiles (box) and 5th/95th (whiskers) are represented. * indicates significant (*P<0.05, **P<0.01, ***P<0.001, ****P<0.0001) increase from baseline. Significant differences between subsequent timepoints are indicated by # (#P<0.05, ##P<0.01, ###P<0.001, ####P<0.0001). Repeated Measures Two-way ANOVA on log-transformed OD (450 nm) values and mixed-effect.

Results are presented as reciprocal endpoint titers. Central bars indicate medians. Hinges indicate quartiles. Whiskers indicate 95% confidence intervals. Significant differences between days for each vaccine regimen are indicated by # (###p<0.001, ####p<0.0001; unpaired T-test of log-transformed values); LLOD, lower limit of detection

CoVLP vaccine candidate + GSK's pandemic adjuvant induced diverse antibody isotypes, as well as neutralizing antibodies in macaques

Cell-mediated Immune Response Profiles of 15 µg of CoVLP Vaccine Candidate + GSK's Pandemic Adjuvant in Macaques

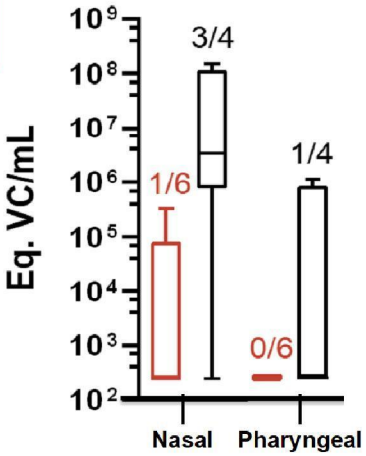


CoVLP vaccine candidate + GSK's pandemic adjuvant induced Th1 and Th2 immune responses in macaques, including a polyfunctional CD4+ response

Percent of S protein specific Total IL-2+, triple positive IL-2+ IFN-γ+ TNF-α+ and Total IL-4+ CD4 in PBMC (Intracellular Cytokine Stain, Flow cytometry) of macaques at baseline, 7 and 21 days after the first and the second IM immunization with 15 µg CoVLP with GSK's pandemic adjuvant. Median (line), 25th/75th percentiles (box) and 5th/95th (whiskers) are represented. * indicate significant (*P<0.05, **P<0.01, ****P<0.0001) differences between timepoints (Kruskal-Wallis).

Viral Loads in Mucosal Swabs 6 Days Post-Infection in Macaques at 28 Days after 2nd Dose of 15 µg of CoVLP Vaccine Candidate + GSK's Pandemic Adjuvant

Animals were challenged with SARS-CoV-2 10^6 pfu



CoVLP + GSK's pandemic adjuvant

Control

- In this challenge assay:
  - Less virus in upper airways after 2 doses with CoVLP vaccine candidate + GSK's pandemic adjuvant
  - No evidence of enhanced disease in vaccinated animals

Medicago Inc. Data on file. Equivalent (Eq.) Viral copy (VC) in nasal, pharyngeal and rectal swabs; ratios indicate the number of animals with detectable SgRNA/total animals in each treatment group. Bars indicate medians and error bars indicate 95% CI

Summary of Non-clinical Findings for CoVLP Vaccine Candidate + GSK's Pandemic Adjuvant

- Humoral and CMI responses induced in both mice & NHP
- Immunogenicity better characterized in NHP (more relevant model for human)
- No safety signals, minor reactogenicity, no treatment-related signs
- Macaques challenged after 2 doses had less virus in upper airways
- No evidence of enhanced disease in vaccinated macaques after challenge

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- **CoVLP Phase 1 results**
- Next steps, CoVLP Development Program

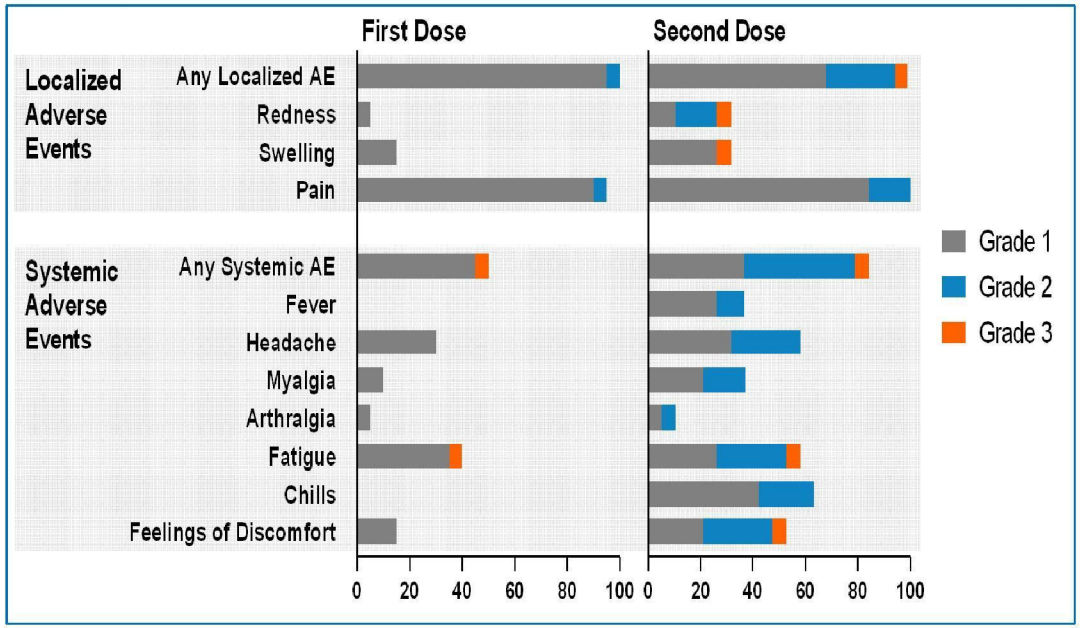
Phase 1 Trial Design in Adults Aged 18-55 Years

A Randomized, Partially-Blinded, Dose-Ranging Phase 1 Study to Assess the Safety, Tolerability, and Immunogenicity of a Recombinant Coronavirus-Like Particle COVID 19 Vaccine in Adults 18-55 Years of Age

Investigational Product	Recombinant Coronavirus-like Particle Vaccine (CoVLP)
Active Substance(s)	Recombinant S protein expressed as virus-like particles (VLP) for the COVID-19 SARS-CoV-2 virus strain
Adjuvant(s)	AS03 (GSK) or CpG1018 (Dynavax)
Dosage and Administration	Two intramuscular injections 21 days apart (Day 0 and Day 21) at three dose levels (3.75 µg, 7.5 µg, and 15 µg VLP) unadjuvanted or adjuvanted
Primary Objectives	Safety and tolerability 21 days after each vaccination; immunogenicity (NAb & CMI) at Days 0, 21 and 42
Secondary Objectives	Anti-S antibody response at days 0, 21 and 42; immunogenicity and safety endpoints at 12-months following the last vaccination
Number of Subjects	180 (20 subjects per group)

NCT04450004

Solicited Adverse Events & Safety Profile 7 Days after 1st or 2nd Dose of 3.75 µg CoVLP Vaccine Candidate + GSK's Pandemic Adjuvant

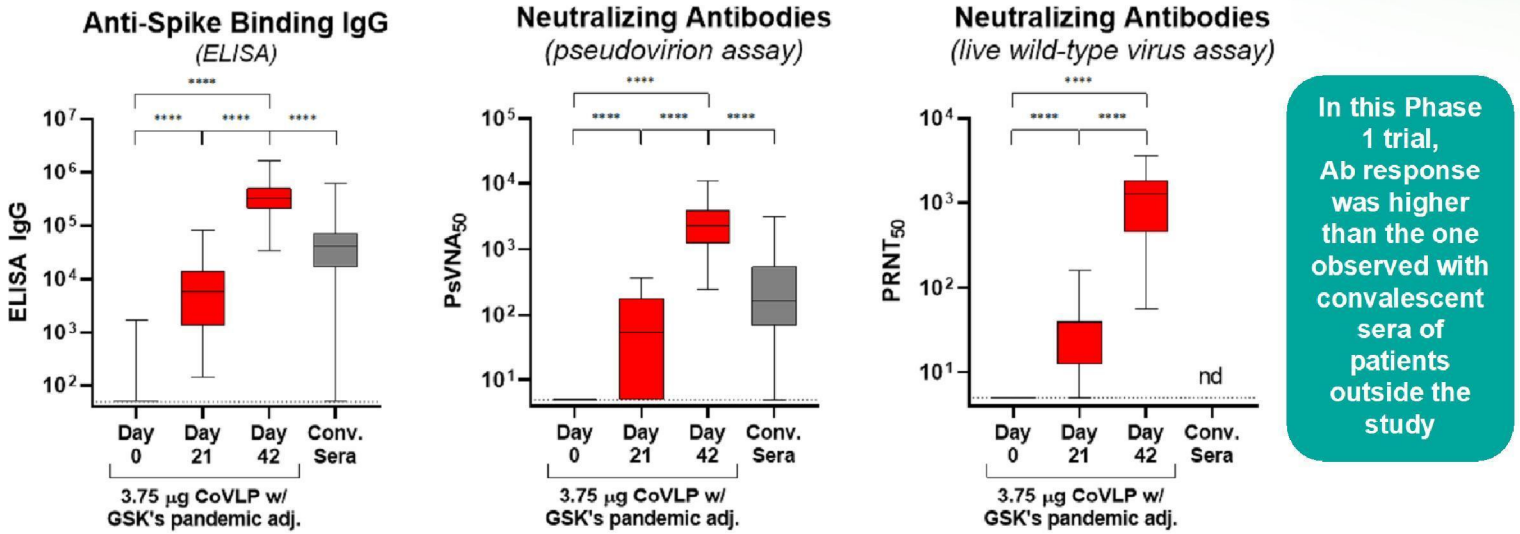


Phase 1 trial in 180 subjects aged 18-55

- No serious adverse events reported
- Unsolicited AE mild or moderate
- No AE of special interest
- No COVID-19 cases
- Data supported by 12 IDMC meetings

Medicago Inc. Data on file. Unsolicited AE included 3 grade 1 (mild) and 1 grade 2 (moderate) events after vaccination one and 5 grade 1 (mild) event after vaccination two.

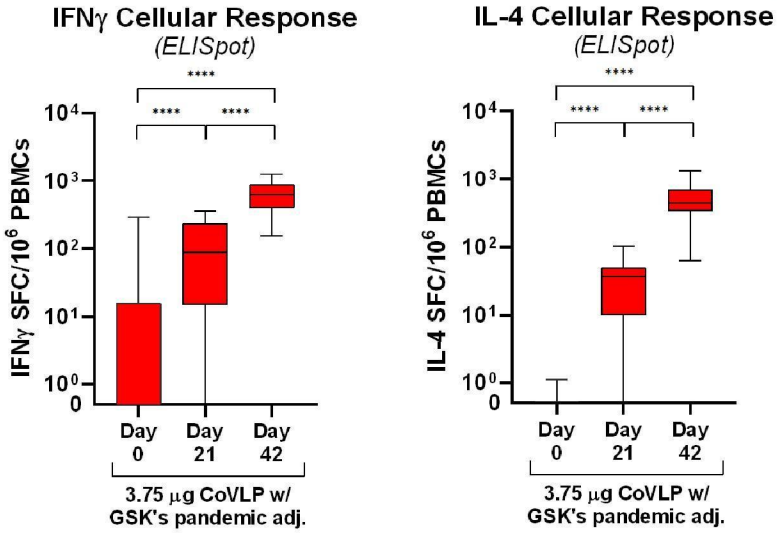
Humoral Immune Response at Day 0 and After 1st or 2nd Dose of 3.75 µg CoVLP Vaccine Candidate + GSK's Pandemic Adjuvant

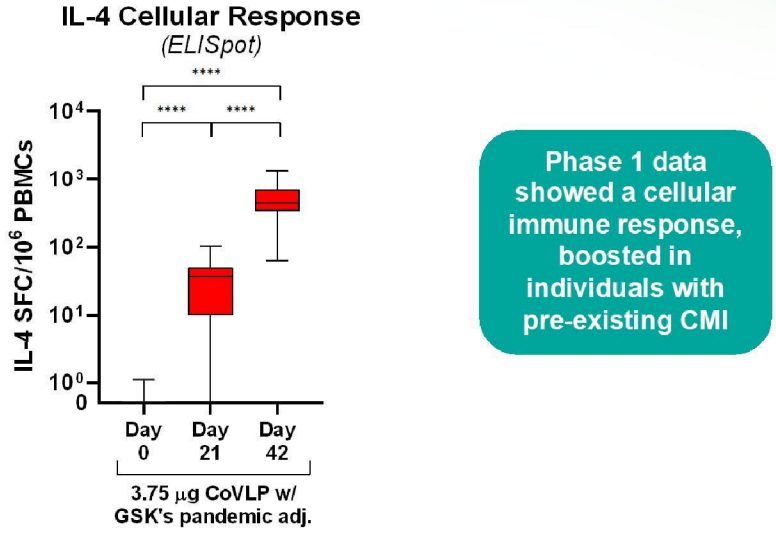


In this Phase 1 trial, Ab response was higher than the one observed with convalescent sera of patients outside the study

Medicago Inc. Data on file. Titers of convalescent sera or plasma obtained from COVID-19 infected patients are shown in grey (N=35). Results are presented as reciprocal endpoint titers. Central bars indicate medians. Hinges indicate quartiles. Whiskers indicate 95% confidence intervals. Significant differences between treatment days are indicated by * (*p<0.0001; paired t test of log-transformed values). Significant differences between day 42 vaccinated individuals and convalescent sera are indicated by * (****p<0.0001; unpaired t test of log-transformed values).

Cellular Immune Response at Day 0 and After 1st or 2nd Dose of 3.75 µg CoVLP Vaccine Candidate + GSK's Pandemic Adjuvant





Phase 1 data showed a cellular immune response, boosted in individuals with pre-existing CMI

Medicago Inc. Data on file. Frequencies of antigen-specific cells IFN-γ and IL-4 cellular immune responses at baseline (day 0) and 21 days after one immunization (day 21) or two immunizations (day 42) with 3.75 µg dose of CoVLP with GSK's pandemic adjuvant after restimulation *ex vivo* with pooled 15mer recombinant spike peptide pool. Bars indicate medians. Hinges indicate quartiles. Whiskers indicate 95% CI. Significant differences between days are indicated by * (****P<0.0001; Between days 0 and 21 or 0 and 42: Mann-Whitney; each test to day 0 pre-vaccination data set that include all 180 experimental subjects. Differences between day 21 and 42 are by Wilcoxon matched pairs signed rank test.)

Summary of Results with CoVLP Vaccine Candidate + GSK's Pandemic Adjuvant

Preclinical

- Humoral and cellular immune responses induced in mice and macaques
- Respiratory viral loads reduced in macaques immunized twice after a challenge with SARS-CoV-2 without indications of enhanced disease

Phase 1 in 18-55

(3.75 µg CoVLP Vaccine Candidate + GSK's Pandemic Adjuvant)

- CoVLP vaccine candidate elicited no safety signals in this study in 18-55 yo, side effects mainly mild to moderate and of short duration
- Antibody levels higher than those observed in convalescent sera, including neutralizing antibody response
- Balanced cellular immune response with GSK's pandemic adjuvant
- Data support moving CoVLP vaccine candidate to Phase 2/3 trial

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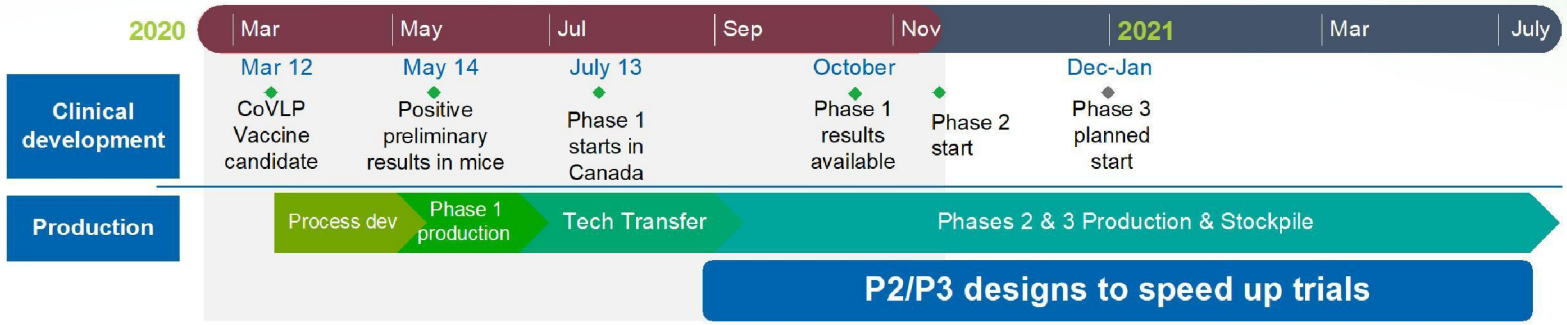
Next Steps of Medicago's CoVLP Vaccine Candidate Development Program



Phase 1 (18-55)

- 180 subjects
- Dose-finding safety and immunogenicity study in seronegative adults
- Dose-escalation, slow enrolment, open-label
- 2 adjuvants, unadjuvanted, 3 dose levels and prime-boost investigated

Phase 2 Nov 2020

- 612 subjects
- Dose confirmation (3.75 µg + GSK's pandemic adjuvant) safety & immunogenicity
- Target populations investigated:
  - Adults 18-64y
  - Older adults
    - 65-74y
    - 75+

Phase 3 Dec 2020 Interim Q2 2021

- 30,000 subjects expected*
- Randomized placebo-controlled study to evaluate efficacy of CoVLP vaccine at prevention of COVID-19 disease
- Global study

Data on file, Medicago Inc.; * younger subjects <18; subjects with co-morbidities and pregnant women planned to be added during Phase 3

Medicago is scaling up its current production capacity to answer global demand

5.1.1c

New global facility under construction in Quebec is expected to be operating

5.1.1c

5.1.1c


Quebec Pilot Plant


Raleigh, North Carolina


Quebec Global Facility

Medicago capacity estimated

5.1.1c

5.1.1c

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Thank you

Medicago collaborators throughout the years