Supplementary Appendix

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This appendix has been provided by the authors to give readers additional information about the work.

Efficacy and Safety of a Recombinant Plant-Based, Adjuvanted COVID-19 Vaccine

SUPPLEMENTARY APPENDIX

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List of Investigators

Country	Investigator	Institution
Argentina	Chirino Navarta, Daniel	Mautalen Salud e Investigación (Expertia SA), Buenos Aires
Argentina	Llapur, Conrado	Clinica Mayo de UMCB SRL, San Miguel de Tucumán
Argentina	Maulen, Sergio	Fundación FunDaMos, Buenos Aires
Argentina	Perez Marc, Gonzalo	Hospital Militar Central Cirujano Mayor Dr. Cosme Argerich, Buenos Aires
Argentina	Polack, Fernando	Hospital Militar Central Cirujano Mayor Dr. Cosme Argerich, Buenos Aires
Argentina	Riera, Fernando	Sanatorio Allende, Cordoba
Brazil	Diaz, Ricardo	Azidus Brasil Pesquisa e Desenvolvimento Ltda, Valinhos, Sao Paulo
Brazil	Ferrara, Luciana	Azidus Brasil Pesquisa e Desenvolvimento Ltda, Valinhos, Sao Paulo
Brazil	Freire, Antonio	Santa Casa De Misericordia De Belo Horizonte, Belo Horizonte, Minas Gerais
Brazil	Hammes, Luciano	Centro de Pesquisa Clinica - Hospital Moinhos de Vento, Porto Alegre, Rio Grande do Sul
Brazil	Itinose, Kengi	Unidade Hospital do Rocio, Campo Largo
Brazil	Nogueira, Mauricio	Fundação Faculdade Regional de Medicina de Sao Jose do Rio Preto, Sao Jose do Rio Preto
Brazil	Vasconcellos, Eduardo Freire	Instituto de Pesquisas Clinicas L2IP, Brasilia, DF
Brazil	Wolff, Priscila Geller	IBPClin Instituto Brasil de Pequisa Clinica, Rio de Janeiro
Canada	Abitbol, Alexander	LMC Clinical Research Inc. (CPU), Toronto, Ontario
Canada	Aggarwal, Naresh	Aggarwal and Associates Ltd, Brampton, Ontario
Canada	Badenhorst, Josias	CARe Clinic, Red Deer, Alberta
Canada	Dionne, Marc	CHU de Québec-Université Laval, Quebec City, Quebec
Canada	Frechette, Andre	Diex Research Quebec Inc, Quebec City, Quebec
Canada	Gauthier, Jean Sebastien	QT Research Sherbrooke, Sherbrooke, Quebec
Canada	Girard, Ginette	Diex Research, Sherbrooke, Quebec
Canada	Henein, Sam	SKDS Research Inc., Newmarket, Ontario
Canada	Libman, Michael	McGill University Health Centre Vaccine Study Centre, Pierrefonds, Quebec

Country	Investigator	Institution
Canada	Paquette, Jean-Sebastien	Diex Recherche Joliette, Saint-Charles-Borromée, Quebec
Canada	Tellier, Guy	Manna Research Mirabel, Mirabel, Quebec
Canada	Vale, Noah	Manna Research Toronto, Toronto, Ontario
Canada	Vallieres, Gerald	Manna Research Quebec, Lévis, Quebec
Canada	Wallace, Garry	Dawson Clinical Research Inc., Guelph, Ontario
Mexico	Castro Melchor, Liliana	Investigación Biomédica para el Desarrollo de Fármacos, S.A. de C.V., Zapopan
Mexico	De los Rios Ibarra, Manuel	Centro para el Desarrollo de la Medicina y de Asistencia Médica Especializada SC, Culiacan
Mexico	Del Carpio, Luis	Sociedad de Metabolismo y Corazon S.C (SOMECO), Veracruz
Mexico	Guzman Romero, Ana Karla	RM Pharma Specialists S.A. de C.V., Ciudad de Mexico
Mexico	Martinez Perez, Jose Miguel	Integra RGH Centro de Investigacion - Clinica de Ozonoterapia RGH AC, Puebla
Mexico	Rios Mejia, Edmundo Daniel	Investigación Biomédica para el Desarrollo de Fármacos, S.A. de C.V., Aguascalientes
Mexico	Sanchez Campos, Efren Alberto	Centro Multidisciplinario para el Desarrollo Especializado de la Investigación Clínica en Yucatan S.C.P. (CEMDEICY S.C.P.), Merida
United Kingdom	Apoola, Ade	University Hospitals Derby and Burton, Derby
United Kingdom	Galloway, James	Kings College Hospital, London
United Kingdom	Healy, Brendan	Public Health Wales NHS Trust, Cardiff
United Kingdom	Kyriakidou, Christina	Synexus Midlands Clinical Research Centre, Birmingham
United Kingdom	Lacey, Charles	University of York/York Teaching Hospital, York
United Kingdom	Moore, Patrick	University Hospitals Dorset NHS Foundation Trust, Bournemouth
United Kingdom	Nicholls, Helen	Synexus Wales Clinical Research Centre DRS, Cardiff
United Kingdom	Prestwell, Carol	Synexus Lancashire Clinical Research Centre DRS, Chorley
United Kingdom	Soiza, Roy	NHS Grampian, Aberdeen
United Kingdom	Viljoen, Marlies	Synexus Manchester Clinical Research Centre DRS, Manchester
United Kingdom	Whittington, Ashley	London North West University Healthcare NHS Trust, Harrow

Country	Investigator	Institution
United States	Aazami, Hessam	Hope Clinical, Canoga Park, California
United States	Adelglass, Jeffrey	Research Your Health, Plano, Texas
United States	Anderson, Duane	Excel Clinical Research, Las Vegas, Nevada
United States	Arora, Samir	Aventiv Research Inc, Columbus, Ohio
United States	Berger, Ira	Meridian Clinical Research, Rockville, Maryland
United States	Bordon, Jose	Ascension Providence Health System, Washington, DC
United States	Bradley, Paul	Meridian Clinical Research, Savannah, Georgia
United States	Carlson, Mark	Be Well Clinical Studies, LLC, Lincoln, Nebraska
United States	Casey, Sherri	Benchmark Research, Covington, Louisiana
United States	Chu, Laurence	Benchmark Research, Austin, Texas
United States	DeFrancisco, Don	Pharmacology Research Institute, Newport Beach, California
United States	Ebuh, Valentine	Global Medical Research, Dallas, Texas
United States	Ensz, David	Meridian Clinical Research, Sioux City, Iowa
United States	Essink, Brandon	Meridian Clinical Research LLC, Omaha, Nebraska
United States	Fiel, Thomas	Fiel Family & Sports Medicine/ CCT Research, Tempe, Arizona
United States	Forte, Dana	Forte Family Practice/ CCT Research, Las Vegas, Nevada
United States	Fussell, Suzanne	Long Beach Clinical Trial Services Inc, Long Beach, California
United States	Gregerson, Gary	ASR, LLC, Nampa, Idaho
United States	Haffizulla, Jason	Precision Clinical Research, LLC, Sunrise, Florida
United States	Hassman, Michael	Hassman Research Institute, Berlin, New Jersey
United States	Hemmersmeier, John	South Ogden Family Medicine/ CCT Research, Ogden, Utah
United States	Hong, Mathew	M3 Wake Research, Inc, Raleigh, North Carolina
United States	Juvvadi, Nikhila	Affinity Health, Chicago, Illinois
United States	Latorre, Agustin	AppleMed Research Inc, Miami, Florida
United States	Martin, Earl	DM Clinical Research/Martin Diagnostic Clinic, Tomball, Texas
United States	Oppong, Yaa	Carolina Institute for Clinical Research, Fayetteville, North Carolina
United States	Patel, Suchet	Meridian Clinical Research, LLC, Endwell, New York
United States	Pickrell, Paul	Tekton Research, Austin, Texas

Country	Investigator	Institution
United States	Rosen, Jeffrey	AMR Miami, formerly Clinical Research of South Florida, Coral Gables, Florida
United States	Rothenberg, Joan	Velocity Clinical Research, Cleveland, Ohio
United States	Schwartz, Howard	Research Centers of America, Hollywood, Florida
United States	Seger, William	Benchmark Research, Fort Worth, Texas
United States	Tarakjian, Denis	WR-MCCR, LLC, San Diego, California
United States	Thakkar, Harish	Mt. Olympus Medical Research LLC, Sugarland, Texas
United States	Vanderzyl, John	Sugar Lakes Family Practice, PA - an Elligo Health Research Site, Sugarland, Texas
United States	Vrbicky, Keith	Meridian Clinical Research LLC, Norfolk, Nebraska
United States	Walters, Alton	Las Vegas Clinical Trials, North Las Vegas, Nevada
United States	Williams, Barton	Trial Management Associates, LLC, Wilmington, North Carolina
United States	Williams, Hayes	Achieve Clinical Research, LLC dba Accel Research Sites at Birmingham Clinical Research Unit, Birmingham, Alabama
United States	Wolf, Thomas	Methodist Physicians Clinic / CCT Research, Fremont, Nebraska
United States	Zeig, Steven	Elixia LLC, Palm Beach, Florida

Supplementary Methods

Context in which the study was performed

The current trial was conducted during active roll-out of emergency-use or approved SARS-CoV-2 vaccines. Although the pace and penetration of these campaigns varied, recruitment of elderly participants and those with comorbidities became progressively more difficult over time, leading to smaller numbers in these populations than originally planned. Furthermore, as vaccine eligibility expanded, a growing number of participants exercised their Protocol-sanctioned option to withdraw or be unblinded to consider accessing another vaccine. This led to progressive loss of participants with a growing imbalance between the CoVLP+AS03 and placebo groups that was managed by using person-year denominators to calculate all efficacy outcomes i.e.: the accrued follow-up time for each participant was considered. Overall, 2712 participants in the placebo group (22.5%) and 600 participants in the CoVLP+AS03 group (5.0%) were unblinded prior to Interim Order/Emergency Use Authorization (IO/EUA) per pre-specified criteria and discontinued prematurely to receive a deployed vaccine. The number of participants who left the study by country for the placebo and CoVLP+AS03 groups were: 744 (15.0%) and 160 (3.2%) in Argentina, 1441 (34.2%) and 150 (3.6%) in Brazil, 417 (61.5%) and 233 (34.5%) in Canada, 53 (37.3%) and 18 (11.9%) in the United Kingdom, 0 (0%) and 0 (0%) in Mexico, and 57 (4.3%) and 39 (2.9%) in the USA. In order to identify cases rapidly during vaccine roll-out, a single symptom COVID-19-compatible was used to trigger PCR testing, likely resulting in the detection of minimally-symptomatic cases. Finally, CoVLP+AS03 was challenged by multiple variants with increased transmissibility, resistance to vaccine-induced immunity or both (Figure S1).

Trial Oversight

The trial is being conducted in accordance with current International Conference on Harmonization (ICH) guidelines on Good Clinical Practice, and applicable country-specific regulatory requirements. All participants provided written informed consent before being enrolled. Appropriate Independent Institutional Review Boards and/or Ethics Committees approved the protocol, protocol amendments and consent forms. Safety and efficacy data were reviewed by an Independent Data Monitoring Committee (IDMC) as needed.

The trial is ongoing, and, at the time of writing, the investigators remained unaware of participant-level treatment assignments. Limited team members have unblinded access to the

data to facilitate submission of clinical safety findings to regulatory agencies and the IDMC. All other trial staff and participants remain unaware of treatment assignments.

The study was designed by Medicago R&D Inc with input from GSK and conducted with the assistance of Syneos Health Canada, including study management, monitoring, medical monitoring, data collection, IDMC and IDMC sub-committee management, and analysis. Site investigators were responsible for subject recruitment, local study conduct and data collection. Key laboratory outcomes were generated by ViroClinics/DDL (Rotterdam, NL: RT-PCR, sequencing and strain assignment). Ultimate responsibility for the integrity and analysis of the data, the writing and review of the manuscript and the decision to submit for publication rests with Medicago R & D Inc with input from GSK. The contributions of individual authors to these activities are provided under *Author Contributions* at the end of the main text.

Safety Oversight

The median duration of time to censoring for the analysis of local and systemic solicited adverse events (ITT) was 3.7 months (25^{th}:75^{th} percentiles 2.9:4.2 months and 3.0 months (25^{th}:75^{th} percentiles 2.0:3.9) months for the CoVLP+AS03 and placebo arms respectively. Safety oversight was provided by the Safety Monitoring Team that reviewed safety data on a regular basis in a blinded manner. This included data on Adverse Events of Special Interest (AESIs) including potential Immune-Mediated Diseases (pIMDs), Medically-Attended Adverse Events (MAAE), Serious Adverse Events (SAE) including anaphylaxis and severe allergic reactions, Vaccine-Associated Enhanced Disease (VAED), or Vaccine-Associated Enhanced Respiratory Disease (VAERD), with triggers in place to escalate to the IDMC if a potential safety signal was identified. In parallel, an unblinded medical monitor reviewed unblinded data on a real-time basis to escalate to the IDMC if a stopping rule was met. The safety and efficacy data were also reviewed by the IDMC, to confirm that the primary vaccine efficacy endpoint had been met, and that the benefit/risk profile was positive.

Trial Vaccine

CoVLP is composed of full-length S glycoprotein from SARS-CoV-2 (strain hCoV-19/USA/CA2/2020) in a pre-fusion stabilized conformation with R667G, R668S, R670S, K971P and V972P modifications, expressed in *Nicotiana benthamiana* by *Agrobacterium*-

based transient transfection. Expression results in formation of S trimers followed by spontaneous budding of 100-150 nm virus-like particles from the plasma membranes of leaf cells. AS03 is an oil-in-water emulsion containing DL-α-tocopherol and squalene (GlaxoSmithKline, Wavre, Belgium). The placebo was composed of 0.5 mL phosphate-buffered saline (PBS) with polysorbate 80.

Preparation of the Vaccine

Immediately prior to use, 2.5 mL of CoVLP and 2.5 mL of AS03 were mixed in a multidose vial to obtain 10 vaccine doses of 0.5 mL each. Each dose of the vaccine contained 3.75 µg of CoVLP formulated in PBS with polysorbate 80, 11.86 mg of DL-α-tocopherol and 10.69 mg of squalene. Once mixed, the combined CoVLP+AS03 was stored at room temperature protected from light and had to be used within 6 hours.

Calculation of Vaccine Efficacy

Symptoms that could trigger SARS-CoV-2 testing included fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting or diarrhea. Vaccine Efficacy (VE) was calculated as 100 × (1 – incidence rate ratio (IRR)) where the IRR is defined as the ratio of person-years rate of COVID-19 cases in the CoVLP+AS03 group relative to cases in the placebo group. For both the Intention-To-Treat (ITT) and Per-Protocol analysis sets, censoring was performed at the earliest of any of the following events: occurrence of virologically-confirmed COVID-19 (date of first symptoms), the database was frozen for the Primary Vaccine Efficacy (PVE) analysis, the date a subject was unblinded, the date a subject received another COVID-19 vaccine, or the date a subject withdrew from the study. The VE success criteria for the PVE endpoint were defined as a ≥50 %-point estimate and a >30 % lower limit of the 95% CI. Assuming the number of cases in each arm followed a Poisson distribution, then conditioning on the total number of cases and the ratio of person-time of follow up, the exact 95% CIs for the IRR, and hence for VE = 1-IRR, was obtained assuming a binomial distribution with mid-P adjustment[1]. VE for secondary endpoints was analyzed using the same methods, except for the success criterion being defined as >0% lower limit of the 95% CI. The widths of confidence intervals for secondary and subgroup analyses have not been adjusted for multiplicity, and hence are best regarded as descriptive.

Cumulative incidence curves were calculated using the Kaplan-Meier method. All data presented in this manuscript are the result of pre-specified outcomes except for VE versus moderate-to-severe disease and the sub-analysis of viral load at diagnosis. Although measurement of viral load post-infection was a pre-specified endpoint, the analysis by sub-group presented herein was not anticipated and should therefore be considered *post hoc*. While analysis of VE against severe disease was anticipated (secondary outcome), the analysis of VE versus moderate-to-severe disease was *post hoc*, driven in large part by the small number of severe cases observed in the study.

For this endpoint-driven vaccine efficacy study, assuming a true vaccine efficacy of 60%, a 1:1 treatment randomization ratio, and expecting the lower limit of the 95% confidence interval of vaccine efficacy of at least 30%, and vaccine efficacy of at least 50%, a sample size of 30,000 subjects with a minimum of 160 COVID-19 cases was estimated to provide at least 90% power.

Protocol for PCR-Testing and Viral Load Analysis

At the current time, viral load (VL) data are available only for the initial (i.e.: diagnostic) nasopharyngeal swab. In this study, PCR testing was triggered by the persistence of ≥1 COVID-19-compatible symptom lasting >24 hours and every attempt was made to obtain this swab as quickly as possible. Because of the anticipated delays in shipping to the central PCR-testing facility in the Netherlands, initial testing included a local test (i.e.: PCR or antigen-capture) as well as swabs for the central laboratory. If the local test was positive, participants were given a kit with enough swabs for every other day self-testing for up to 14 days to permit assessment of VL over time (i.e.: intensity and duration of viral shedding). The analysis of these swabs is under way and will be reported separately. Only the PCR testing performed by the central laboratory was used for defining the primary vaccine efficacy analysis set and for the VL calculations presented herein. The VL was determined using PCR targeting the nucleocapsid gene. Primers and assay conditions were based on the CDC N1 assay[2]. The resulting cycle threshold (Ct) values were plotted against a four-point standard curve run simultaneously with test samples and converted to $\log_{10}$ copies/mL (cp/mL). Viral load values under the detection limit (2.08 log10) were set to half of that limit.

Rationale for Viral Load Analysis

Analysis of viral load was a pre-specified secondary outcome of the study to assess both the intensity and duration of viral shedding in CoVLP+AS03 versus Placebo recipients. To achieve this outcome, swabs collected every other day for up to 14 days after an initial positive PCR were to be used to assess the viral burden from diagnosis until clearance (i.e.: area under the curve). The analysis of viral load at diagnosis and comparison between groups and sub-groups presented in this work was prompted by the unexpected observation of a 2-fold difference between sequencing success between breakthrough cases in the CoVLP+AS03 arm of the study and placebo cases. As a result, the VL data presented here represent only a part of a secondary outcome and their more detailed analysis goes beyond what was anticipated in the Statistical Analysis Plan (Appendix: SAP). As a result, these analyses should be considered, at least partially, *post hoc*.

Viral Sequencing

Sequencing of viral genomes from swabs was performed by Viroclinics-DDL (Netherlands). Total nucleic acid (DNA/RNA) isolation was performed with the MagMAX™ Viral/Pathogen Nucleic Acid Isolation kit on the KingFisher™ Flex instrument (ThermoFisher) using 400 µL sample input. Nucleic acid elution was performed in 50 µL of elution buffer. Full-length amplification of the target RNA, i.e., RNA encoding SARS-CoV-2 spike (S) protein, was performed by amplifying 5 overlapping fragments of ~900 bp by nested RT-PCR using the primer sets from the CDC Singleplex PCR 38 amplicons protocol (PacBio). The outer one-step RT-PCR was performed with the outer S-gene primer sets and the SuperScript™ III One-Step RT-PCR System with Platinum™ Taq High Fidelity DNA Polymerase (ThermoFisher) using 5 µL of the isolated RNA. The nested (inner) amplification step was performed with the inner primer sets and the Phusion Hot Start II High-Fidelity DNA Polymerase (ThermoFisher) or Q5® Hot Start High-Fidelity DNA Polymerase (NEB). Nested PCR products were analyzed by gel electrophoresis using standard molecular biology protocols, to confirm successful amplification.

Next-generation sequence (NGS) analysis of S-gene amplicons was performed using the MiSeq or NextSeq Illumina platforms. NGS analysis was performed on samples consisting of two pools of non-overlapping S-gene amplicons. To generate single datasets for reporting and interpretation, the FASTQ files of the two pools of non-overlapping fragments were pooled together *in silico*. After combining the two datasets, all data was mapped against the same

reference sequence (SARS-CoV-2 Wuhan-Hu-1 GenBank: MN908947.3). Identifying the location on the reference genome allowed identification of reads that started or ended in or near a primer region (possibly containing primer ambiguity) in order to select them for the primer trimming algorithm. Sufficient nucleotides were trimmed off each read that was selected by this process and the remaining part of the read was considered non-primer derived. For *in silico* pooling and primer trimming, all primer locations were implemented in DDL's bioinformatics ATHENA pipeline. The deep sequencing process comprised: quantification of S-gene amplicon pools by PicoGreen or Qubit™; fragment dilutions and equimolar mixing to normalize the concentrations of each of the amplicon pools; library preparation with the Nextera XT System (Illumina); sequence reactions with 300-cycle kit (150 bp bidirectional reads) on the Illumina Miseq or with a 300-cycle mid output kit on the Illumina Nextseq; Data QC and Data reporting.

Statistical Considerations

As noted above, all efficacy calculations reported herein used 'person-years' as the denominator to adjust for an anticipated asymmetrical loss of placebo recipients compared to CoVLP+AS03 recipients through withdrawal and Protocol-sanctioned unblinding to access a deployed vaccine. At the time the study was performed, vaccines were available for older individuals and for people with high-risk comorbidities in most countries - explaining the smaller than expected number of these individuals in the study. As deployed vaccines became available for healthy, younger adults, many of those enrolled requested unblinding or simply withdrew from the study, presumably to access a vaccine although these data are not available for most subjects who left the study. It is logical that more of those who discovered they had received placebo left the study, leading to the imbalance between the Per Protocol group numbers over time. We have little personal/professional information for study participants so cannot assess either their likelihood of exposure (e.g.: living situation, front-line or healthcare worker) or their level of risk behaviour or risk tolerance (e.g.: likelihood of high-risk behaviours, gamesmanship related to study participation). Although such asymmetric loss of subjects from one study arm has the potential to introduce bias, data contributing to VE estimates were censored for all subjects at the time of unblinding even if they chose not to receive a deployed vaccine and to remain in the study.

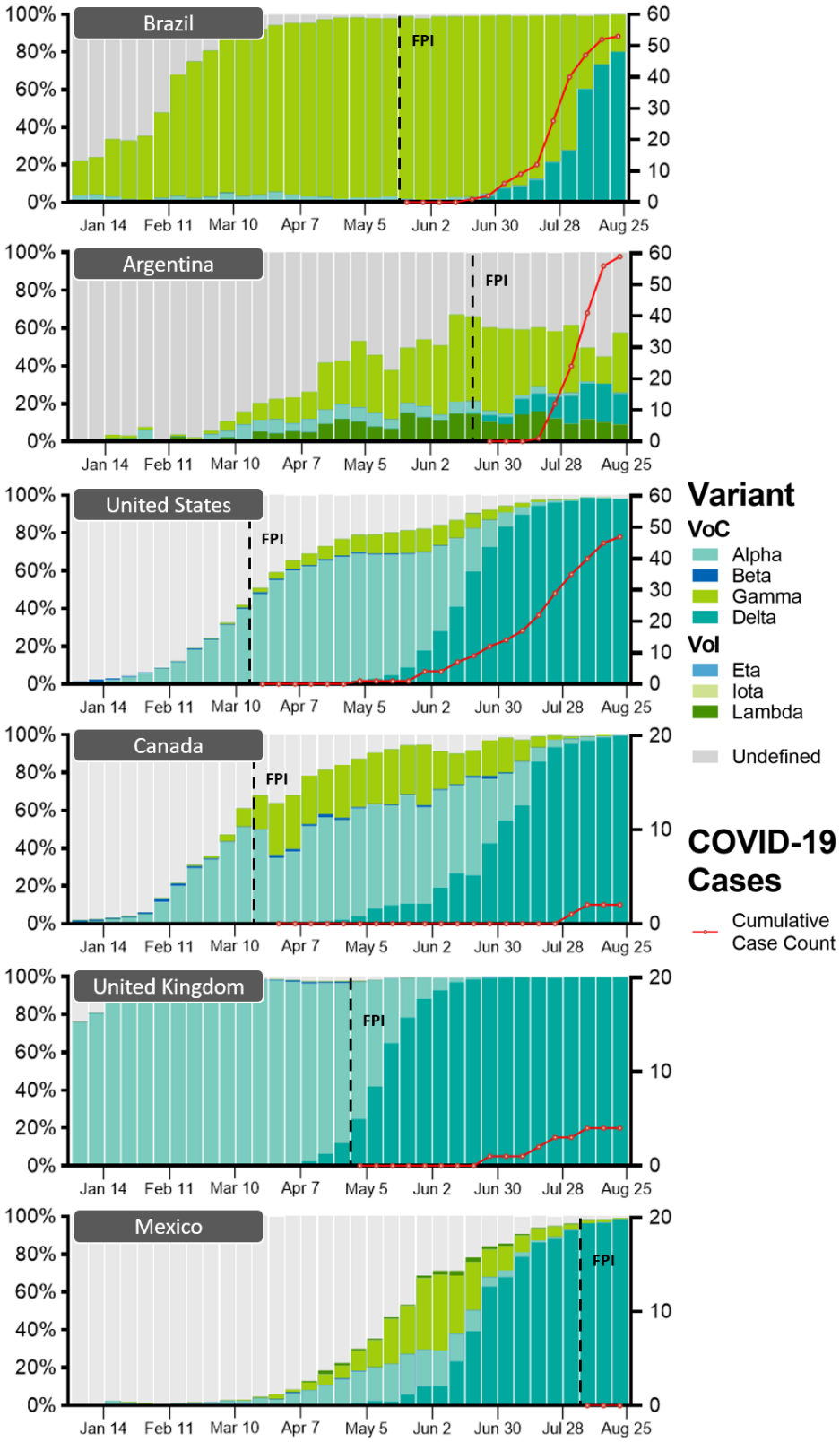
An analysis of the participants who chose to unblind/withdraw and those who chose to remain in the study was conducted and no major differences were identified either within or between

groups in terms of age, sex, race/ethnicity, or geography (Table S6). The median period of time to censoring for the vaccine efficacy analysis was fairly even between both treatment groups: 1.5 months in the CoVLP recipients (25^{th} and 75^{th} percentiles: 0.8 and 2.0 months) and 1.4 months in the placebo recipients (25^{th} and 75^{th} percentiles: 0.8 and 1.9 months) in the ITT set. The corresponding values for the medians and 25^{th}:75^{th} percentiles for the per protocol set were 1.5 and 0.9:2.0 months the for CoVLP+AS03 group and 1.5 and 0.9:1.9 months for the placebo group.

The variant-specific efficacy analyses reported in this work are somewhat optimistic, in that the samples which could not be sequenced had, as a group, lower associated efficacy than those for which sequencing was successful. We therefore conducted a sensitivity analysis consisting of a 'hot deck' imputation incorporating calendar time, participant country of residence, and trial arm. In the first step, the sequenced data were put into cells formed by a cross tabulation of the quintiles of calendar time of sample collection and country. Then for each cell, the proportional distribution across variants was used to allocate the non-sequenced samples in each cell (resulting mainly in fractional cases). In the next step, the statistician doing the calculations unblinded the CoVLP:Placebo distribution in each cell, to further split each cell's imputed contents in two. Finally, the imputed case contributions for each variant in each arm were summed over its 20 time-country cells, added to the corresponding totals of the known sequences, and then used to calculate efficacy by variant (Table S8).

Supplementary Figure S1 | Circulating Variants During Course of Clinical Trial

Each panel illustrates the variants circulating in time relative to the accrual of symptomatic COVID-19 cases for each nation in which the trial took place. Individual vertical columns indicate the incidence rate of variants reported to GISAID during a seven-day period relative to the total number of sequences reported for the period. Individual colors within the stacked columns represent variants in circulation as a percentage of total, shown on the left Y axis. In cases where sequence identity was not reported or does not refer to a Variant of Concern (VoC) or Variant of Interest (VoI), the incidence was reported as undefined. Red lines indicate the number of total adjudicated COVID-19 cases contributing to the calculation of primary vaccine efficacy accrued in each nation over time as a proportion of the total 165 cases (ITT set: right Y-axis). No COVID-19 cases accrued in Mexico. Dotted vertical lines indicate the date of first injection of a participant by country. FPI: First Patient In.


Brazil
Argentina
United States
Canada
United Kingdom
Mexico
FPI
100%
80%
60%
40%
20%
0%
60
50
40
30
20
10
0
Jan 14
Feb 11
Mar 10
Apr 7
May 5
Jun 2
Jun 30
Jul 28
Aug 25
Variant
VoC
Alpha
Beta
Gamma
Delta
VoI
Eta
Iota
Lambda
Undefined
COVID-19 Cases
Cumulative Case Count

Supplementary Table S1 | Primary, Secondary and Exploratory Objectives of the Study

At the time of writing, the Phase 3 portion of this study is on-going and the data for several of the secondary and exploratory outcomes are not yet available for analysis. The results presented in this work represent efficacy and safety data up to the cut-off points of August 20th and October 25th, 2021 respectively and are indicated in italics in the Table below. Analyses of later time-points and other outcomes will be reported separately.

Primary Outcome	• *Evaluation of the efficacy of CoVLP+AS03 compared to placebo, to prevent PCR-confirmed symptomatic COVID-19 starting 7 days after the 2nd dose at the time of the primary vaccine efficacy (PVE) analysis. The criteria for triggering the PVE analysis were identification of ≥160 COVID-19 cases with a median safety follow-up of ≥2 months post-administration of the 2nd dose of ≥3000 subjects in each of the CoVLP formulation and placebo groups.*
Secondary Outcomes	• Evaluation of the efficacy of CoVLP+AS03 versus placebo at the time of the PVE analysis: - *to prevent severe COVID-19 disease starting 7 days after the 2nd dose;* - to prevent PCR-confirmed symptomatic SARS-CoV-2 infection starting after the first vaccination and during the following intervals: i) after the 1st dose and prior to the 2nd dose; ii) after the 2nd dose and prior to 7 days post-2nd dose; - *to prevent of PCR-confirmed symptomatic SARS-CoV-2 infection by strain starting 7 days after the 2nd dose;* - *to assess the duration and intensity of viral shedding as well as symptoms after PCR-confirmed SARS-CoV-2 infection.* • Evaluation of the efficacy of CoVLP+AS03 versus placebo to prevent PCR-confirmed asymptomatic COVID-19 at Day 201 in D0 seronegative subjects. • Measurement of the following immunogenicity outcomes:

	- In all subjects: Nab titers at Day 0 and Day 42. - In an immunogenicity subset: Nab titers at Day 21, Day 201 and Day 386; IgG (ELISA) titers at Day 42, Day 201 and Day 386; the ratio of Nab titers:IgG (ELISA) titers at Day 21, Day 42, Day 201 and Day 386; IFN-γ and IL4 ELISpot response at Day 42, Day 201 and Day 386. • *Assessment of the safety and tolerability of the CoVLP formulation up to the end of the study.*
Exploratory Outcomes	• Evaluation of the efficacy of CoVLP+AS03 compared to placebo to prevent severe COVID-19 disease by strain ≥7 days after the 2nd dose at the time of the PVE analysis. • Evaluation of specific cell-mediated immune (CMI) response induced by CoVLP+AS03 against the SARS-CoV-2 at Day 42, Day 201 and Day 386 as measured by the percentage of CD4+ T cells expressing functional markers.

Supplementary Table S2 | Summary of Demographics in the Intention to Treat (ITT) Set

'N' is the number of participants in a population, while 'n' represents the number of participants in a category. Race and/or ethnic group were reported by the participants, who could have listed more than one category. SD: Standard deviation; Min: Minimum; Max: Maximum.

	Healthy Adults		Older Adults (65+)		Adults with Comorbidities		All Participants	
	CoVLP+ AS03	Placebo	CoVLP+ AS03	Placebo	CoVLP+ AS03	Placebo	CoVLP+ AS03	Placebo
Participants (N)	10,816	10,835	62	65	1195	1166	12,074	12,066
Sex, n (%)								
Male	5,460 (50.5)	5,553 (51.3)	35 (56.5	35 (53.8)	612 (51.2)	598 (51.3)	6,107 (50.6)	6,186 (51.3)
Female	5,356 (49.5)	5,282 (48.7)	27 (43.5)	30 (46.2)	583 (48.8)	568 (48.7)	5,966 (49.4)	5,880 (48.7)
Race, n (%)								
American Indian / Alaska Native	27 (0.2)	23 (0.2)	0	0	3 (0.3)	7 (0.6)	30 (0.2)	30 (0.2)
Asian	137 (1.3)	137 (1.3)	1 (1.6)	0	11 (0.9)	10 (0.9)	149 (1.2)	147 (1.2)
Black / African American	681 (6.3)	667 (6.2)	8 (12.9)	13 (20.0)	160 (13.4)	155 (13.3)	849 (7.0)	835 (6.9)
Multiple	197 (1.8)	237 (2.2)	1 (1.6)	0	26 (2.2)	26 (2.2)	224 (1.9)	263 (2.2)
Native Hawaiian or Other Pacific Islander	24 (0.2)	21 (0.2)	0	0	2 (0.2)	4 (0.3)	26 (0.2)	25 (0.2)
White or Caucasian	9,694 (89.6)	9,690 (89.4)	51 (82.3)	51 (78.5)	981 (82.1)	959 (82.2)	10,726 (88.8)	10,700 (88.7)
Other	1 (<0.1)	2 (<0.1)	0	0	0	0	1 (<0.1)	2 (<0.1)
Not Reported	52 (0.5)	54 (0.5)	0	1 (1.5)	10 (0.8)	5 (0.4)	62 (0.5)	60 (0.5)
Ethnicity, n (%)								
Hispanic or Latinx	8,965 (82.9)	8,955 (82.6)	15 (24.2)	26 (40.0)	915 (76.6)	915 (78.5)	9,895 (82.0)	9,896 (82.0)
Not Hispanic or Latinx	1,800 (16.6)	1,830 (16.9)	47 (75.8)	39 (60.0)	273 (22.8)	241 (20.7)	2,120 (17.6)	2,110 (17.5)
Not Reported / Specified	51 (0.5)	50 (0.5)	0	0	7 (0.6)	10 (0.9)	58 (0.5)	60 (0.5)
Age at consent (years)								
Mean (SD)	32.0 (11.07)	31.9 (11.02)	69.9 (4.15)	69.5 (5.00)	38.8 (13.72)	39.2 (14.14)	32.8 (11.82)	32.8 (11.85)
Median	29.0	29.0	69.0	68.0	37.0	38.0	29.0	29.0
Min, Max	18, 64	18, 64	65, 80	65, 86	18, 82	18, 86	18, 82	18, 86

Supplementary Table S3 | Summary of Demographics in the Per Protocol set

'N' is the number of participants in a population, while 'n' represents the number of participants in a category. Race and/or ethnic group were as reported by the participants (who could have listed more than one category). SD: Standard deviation; Min: Minimum; Max: Maximum.

	Healthy Adults		Older Adults (65+)		Adults with Comorbidities		All Participants	
	CoVLP+ AS03	Placebo	CoVLP+ AS03	Placebo	CoVLP+ AS03	Placebo	CoVLP+ AS03	Placebo
Participants (N)	9,541	8,609	55	54	958	873	10,554	9,536
Sex, n (%)								
Male	4,764 (49.9)	4,324 (50.2)	30 (54.5)	27 (50.0)	474 (49.5)	441 (50.5)	5,268 (49.9)	4,792 (50.3)
Female	4,777 (50.1)	4,285 (49.8)	25 (45.5)	27 (50.0)	484 (50.5)	432 (49.5)	5,286 (50.1)	4,744 (49.7)
Race, n (%)								
American Indian / Alaska Native	21 (0.2)	15 (0.2)	0	0	1 (0.1)	4 (0.5)	22 (0.2)	19 (0.2)
Asian	116 (1.2)	94 (1.1)	1 (1.8)	0	9 (0.9)	7 (0.8)	126 (1.2)	101 (1.1)
Black / African American	449 (4.7)	434 (5.0)	7 (12.7)	9 (16.7)	101 (10.5)	97 (11.1)	557 (5.3)	540 (5.7)
Multiple	177 (1.9)	183 (2.1)	1 (1.8)	0	22 (2.3)	17 (1.9)	200 (1.9)	200 (2.1)
Native Hawaiian or Other Pacific Islander	19 (0.2)	14 (0.2)	0	0	2 (0.2)	4 (0.5)	21 (0.2)	18 (0.2)
White or Caucasian	8,720 (91.4)	7,835 (91.0)	45 (81.8)	45 (83.3)	817 (85.3)	743 (85.1)	9,582 (90.8)	8,623 (90.4)
Other	1 (<0.1)	1 (<0.1)	0	0	0	0	1 (<0.1)	1 (<0.1)
Not Reported	35 (0.4)	29 (0.3)	0	0	5 (0.5)	1 (0.1)	40 (0.4)	30 (0.3)
Ethnicity, n (%)								
Hispanic or Latinx	8,076 (84.6)	7,171 (83.3)	13 (23.6)	22 (40.7)	761 (79.4)	698 (80.0)	8,850 (83.9)	7,891 (82.7)
Not Hispanic or Latinx	1,428 (15.0)	1,409 (16.4)	42 (76.4)	32 (59.3)	196 (20.5)	171 (19.6)	1,666 (15.8)	1,612 (16.9)
Not Reported / Specified	37 (0.4)	29 (0.3)	0	0	1 (0.1)	4 (0.5)	38 (0.4)	33 (0.3)
Age at consent (years)								
Mean (SD)	31.8 (10.98)	31.9 (11.13)	69.9 (4.30)	69.8 (5.09)	38.7 (13.74)	40.2 (14.37)	32.6 (11.72)	32.9 (12.01)
Median	29.0	29.0	69.0	68.0	37.0	39.0	29.0	29.0
Min, Max	18, 64	18, 64	65, 80	65, 86	18, 82	18, 86	18, 82	18, 86

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Supplementary Table S4 | Baseline Comorbidities

'N' is the total number of participants who received a given vaccination. 'n' is the number of a participants who reported the specified comorbid condition and is shown as a percentage in brackets. Comorbidities reported for ≤0.1% of the total population have not been included.

n (%)	CoVLP+AS03 N = 12036	Placebo N = 12040	Total N = 24076
Participants with at least one comorbidity	**1781 (14.8)**	**1686 (14.0)**	**3467 (14.4)**
Obesity	1246 (10.4)	1171 (9.7)	2417 (10.0)
Documented Hypertension	340 (2.8)	322 (2.8)	672 (2.8)
Type 2 Diabetes	116 (1.0)	100 (0.8)	216 (0.9)
Chronic Obstructive Lung disease (COPD)	41 (0.3)	45 (0.4)	86 (0.4)
Immunocompromised	48 (0.4)	40 (0.3)	88 (0.4)
Cardiovascular disease	40 (0.3)	41 (0.3)	81 (0.3)
Asthma	25 (0.2)	17 (0.1)	42 (0.2)

Supplementary Table S5 | Representativeness of Study Participants

Vaccine Efficacy and Safety after 2 doses of CoVLP+AS03 vaccine candidate	
Special considerations related to	
Gender	A gender effect has been observed resulting in higher risk to develop severe disease in males[3-7]. Although gender effects on immune responses are well documented, no statistically significant gender effects have been reported on either immunogenicity or efficacy of COVID-19 vaccines or candidate vaccines to our knowledge.
Age and Comorbidities	Elderly and people with comorbidities are more susceptible to complications and severe COVID-19[3,7,8]. Comorbidities including, but not limited to, obesity, diabetes, renal failure, hypertension, cardiovascular or chronic obstructive pulmonary diseases, can significantly worsen clinical outcome during COVID-19. Vaccine efficacy and immunogenicity may decrease with age although no statistically significant age-related reduction in vaccine efficacy has been reported with currently used COVID-19 vaccines or vaccine candidates during phase 3 clinical trials.
Race or Ethnic groups	In the United States, African American and Hispanic/Latinx individuals were generally over-represented (although relative representation varied over the waves and depending on the variants) in cases, hospitalizations and deaths; mainly due to socio-economic factors and over-representation of these populations among frontline healthcare workers[3,9].
Overall Representativeness of this Trial	Both sexes are equally represented in our study. Adults with comorbidities represent 9.8% of the subjects in our study (9.7% Placebo versus 9.9% Active Vaccine). Due to active vaccine roll-out in elderly prior to and at the time of this study, people aged ≥65 years only represent 0.53% of our study population. Participants reporting Hispanic/Latinx ethnicity represented >80% of the study population illustrating the contribution of clinical sites located in South America. Despite efforts to locate study sites in areas with high Black or African Americans populations and active outreach, there was a lower willingness to participate in the vaccine clinical trial resulting into a lower than expected enrolment (5.5%) among that population as has been seen in other phase 3 studies[10].
Note: The potential impacts of age, comorbid conditions and sex on clinical co-outcomes were clearly identified during the early stages of the pandemic and were taken into consideration in designing this clinical trial. The possible impact of race or ethnic groups is strongly influenced by socio-economic factors and often depends on the geographic area. In this table, we focused on the situation in the United States. The information summarized in this table was obtained by interrogating large databases including PubMed, CDC website, the WHO website and MedRxiv with *ad hoc* terms including 'gender or gender impact/effect', sex or sex impact/effect', 'comorbidity or comorbid conditions', 'elderly or age effect/impact', 'risk factors', 'at risk populations' combined with 'COVID-19'. References are provided to support selected statements.	

Supplementary Table S6 | Demographics According to Study Discontinuation

'N' is the number of participants in a population (ITT for demographics, SAS for safety analysis set), while 'n' represents the number of participants in a category. Race and/or ethnic group were as reported by the participants (who could have listed more than one category). The 'discontinued' population includes individuals who left the study due to adverse events, death, loss to follow-up, non-compliance, physician/investigator decision, sponsor decision, withdrawal of consent, withdrawal to receive a deployed vaccine, or for other reasons. This population does not include individuals who discontinued for unknown reasons (see Figure 1). Two individuals in the ITT set could not be attributed to the 'discontinued' or 'continued' groups. SD: Standard deviation; Min: Minimum; Max: Maximum; AE: Adverse Event.

	DISCONTINUED		CONTINUED	
	CoVLP+ AS03	Placebo	CoVLP+ AS03	Placebo
Participants in ITT (N)	**1,507**	**4,566**	**10,566**	**7,500**
Sex, n (%)				
Male	827 (54.9)	2,405 (52.7)	5,280 (50.0)	3,719 (49.6)
Female	680 (45.1)	2,161 (47.3)	5,286 (50.0)	3,781 (50.4)
Race, n (%)				
American Indian/ Alaska Native	9 (0.6)	13 (0.3)	21 (0.2)	17 (0.2)
Asian	39 (2.6)	96 (2.1)	110 (1.0)	51 (0.7)
Black/ African American	200 (13.3)	319 (7.0)	649 (6.2)	516 (6.9)
Multiple	21 (1.4)	159 (3.5)	203 (1.9)	104 (1.4)
Native Hawaiian or Other Pacific Islander	4 (0.3)	16 (0.4)	22 (0.2)	9 (0.1)
White or Caucasian	1,222 (81.1)	3,927 (86.0)	9,504 (90.0)	6,773 (90.4)
Other	0	2 (<0.1)	1 (<0.1)	0
Not Reported	12 (0.8)	34 (0.7)	50 (0.5)	26 (0.4)
Ethnicity, n (%)				
Hispanic or Latinx	913 (60.6)	3,548 (77.7)	8,982 (85.0)	6,348 (84.6)
Not Hispanic or Latinx	579 (38.4)	987 (21.7)	1,541 (14.6)	1,123 (15.0)
Not Reported/ Specified	15 (1.0)	31 (0.7)	43 (0.4)	29 (0.4)
Age at consent (years)				
Mean (SD)	33.2 (11.8)	30.3 (10.1)	32.8 (11.8)	34.3 (12.6)
Median	30	27	29	31
Min, Max	18, 73	18, 79	18, 82	18, 86
Solicited AEs				
Participants in SAS (N)	536	1,794	3,600	1,889
≥1 Solicited Local AE	478 (89.2)	862 (48.0)	3,341 (92.8)	815 (43.1)
≥1 Solicited Systemic AE	465 (86.8)	1223 (68.2)	3,147 (87.4)	1,171 (62.0)
≥Grade 3 Solicited AE	30 (5.6)	22 (1.2)	223 (6.2)	23 (1.2)

Supplementary Table S7 | Efficacy by Subgroup (Per Protocol Set)

For most subgroups, values indicate the number of positive cases and total number of participants in the subgroup. Numbers in parenthesis indicate the incidence rate per person years. For variants, values indicate number of sequenced cases assigned to the variant and in parenthesis the incidence rate per person years. Yrs indicate years, 95% CI indicates 95% confidence interval, VE indicates Vaccine Efficacy and NA indicates not applicable.

Subgroup	Placebo	CoVLP+AS03	VE (95% CI)
	# pos/# in subgroup (incidence rate)		
All Participants	118/9,536 (0.179)	39/10,554 (0.052)	71.0 (58.7, 80.0)
Baseline Health, Age			
Healthy, ≥18 to <65 yrs	106/8,609 (0.179)	35/9,541 (0.052)	70.9 (57.7, 80.4)
Healthy, ≥65 yrs	1/54 (0.119)	1/55 (0.097)	18.4 (-3083.7, 97.9)
Significant comorbidities, ≥18 yrs	11/873 (0.187)	3/958 (0.043)	76.8 (21.5, 94.8)
Sex			
Male	56/4,792 (0.158)	21/5,268 (0.052)	67.0 (46.0, 80.4)
Female	62/4,744 (0.204)	18/5,286 (0.052)	74.7 (57.8, 85.4)
Race or Ethnic Group			
Asian	2/101 (0.135)	0/126 (0)	100.0 (-153.3, NA)
Black or African American	8/540 (0.116)	4/557 (0.055)	52.6 (-56.7, 87.6)
White or Caucasian	101/8,623 (0.183)	34/9,582 (0.054)	70.7 (57.1, 80.4)
Latinx or Hispanic	85/7,891 (0.081)	30/8,850 (0.027)	71.0 (56.4, 81.2)
Not Latinx or Hispanic	33/1,612 (0.066)	9/1,666 (0.017)	74.0 (47.1, 88.3)
Disease Severity			
Moderate	30/9,536 (0.046)	8/10,554 (0.011)	76.6 (50.5, 90.0)
Moderate/Severe	32/9,536 (0.049)	8/10,554 (0.011)	78.1 (53.9, 90.5)
Severe	2/9,536 (0.003)	0/10,554 (0)	100 (-204.4, NA)
Seropositivity at Baseline			
Seropositive	3/1,390 (0.036)	6/1,461 (0.069)	-88.8 (-825.1, 53.0)
Seronegative	114/8,033 (0.200)	32/8,975 (0.049)	75.6 (64.2, 83.7)
Variants			
Ancestral	0 (0)	0 (0)	NA
Alpha	5 (0.008)	0 (0)	100 (28.0, NA)
Beta	0 (0)	0 (0)	NA
Gamma	46 (0.070)	6 (0.008)	88.6 (74.6, 95.6)
Delta	39 (0.059)	11 (0.015)	75.3 (52.8, 87.9)
Lambda	3 (0.005)	0 (0)	100.0 (-50.3, NA)
Mu	4 (0.006)	0 (0)	100 (2.3, NA)
Omicron	0 (0)	0 (0)	NA
Sequencing Failure	7 (0.011)	14 (0.001)	-128 (-615.0, 16.4)

Supplementary Table S8 | Redistribution of Sequencing Failures among Variants

Because 12.7% of the cases could not be sequenced and sequencing failures were not evenly distributed between CoVLP+AS03 and placebo arms, we conducted a sensitivity analysis to assess the possible impact of the missing data on variant-specific efficacy estimates. This analysis consisted of a "hot deck" imputation incorporating calendar time, participant country of residence, and trial arm. In the first step, the sequenced data were put into cells formed by a cross tabulation of the quintiles of calendar time of sample collection and country. Then for each cell, the proportional distribution across variants was used to allocate the non-sequenced samples in each cell (resulting mainly in fractional cases). In the next step, the statistician doing the calculations (LM) unblinded the CoVLP:Placebo distribution in each cell, to further split each cell's imputed contents in two. Finally, the imputed case contributions for each variant in each arm were summed over its 20 time-country cells, added to the corresponding totals of the known sequences, and then used to calculated efficacy by variant.

Variant	Observed Placebo Cases	Observed CoVLP +AS03 Cases	Observed Efficacy (%)	Imputed Placebo Cases	Imputed CoVLP +AS03 Cases	Imputed Efficacy (%)
Alpha	6	0	100.0	6.1	0.6	91.0
Gamma	47	6	87.8	50.1	14.9	71.6
Delta	44	12	74.0	45.6	17.3	63.8
Lambda	3	0	100.0	3.1	0.9	72.0
Mu	4	0	100.0	4.0	0.3	92.5
Sequencing Failure	7	14				
Total	111	32	72.5	108.9	34.0	70.2

Supplementary Table S9 | Incidence of Solicited Local Adverse Events (SAS)

'N' is the total number of participants in the Safety Analysis Set (SAS) who received a given vaccination. 'n' is the number of a participants reporting at least 1 occurrence of the specified event category and is shown as a percentage in brackets. For each category, Grade 1 = Mild; Grade 2 = Moderate; Grade 3 = Severe; Grade 4 = Potentially life threatening. If a participant had the same AE but with different grades over time, the highest grade was reported. 'Missing' rows counted participants within the population if they did not have a non-missing assessment or had an assessment with a non-graded value.

n (%)	Vaccination 1		Vaccination 2		Overall	
	CoVLP+ AS03	Placebo	CoVLP+ AS03	Placebo	CoVLP+ AS03	Placebo
	N = 4 136	N = 3 683	N = 4 136	N = 3 683	N = 4 136	N = 3 683
≥1 solicited local AE	**3538 (85.5)**	**1149 (31.2)**	**3496 (84.5)**	**1135 (30.8)**	**3819 (92.3)**	**1677 (45.5)**
Grade 1	3021 (73.0)	1123 (30.5)	2494 (60.3)	1111 (30.2)	2590 (62.6)	1629 (44.2)
Grade 2	484 (11.7)	24 (0.7)	917 (22.2)	23 (0.6)	1115 (27.0)	45 (1.2)
Grade 3	33 (0.8)	2 (<0.1)	85 (2.1)	1 (<0.1)	114 (2.8)	3 (<0.1)
Grade 4	0	0	0	0	0	0
Missing	4 (<0.1)	6 (0.2)	74 (1.8)	12 (0.3)	2 (<0.1)	5 (0.1)
Pain	**3514 (85.0)**	**1082 (29.4)**	**3483 (84.2)**	**1100 (29.9)**	**3806 (92.0)**	**1604 (43.6)**
Grade 1	3072 (74.3)	1066 (28.9)	2625 (63.5)	1080 (29.3)	2758 (66.7)	1570 (42.6)
Grade 2	420 (10.2)	15 (0.4)	830 (20.1)	20 (0.5)	999 (24.2)	33 (0.9)
Grade 3	22 (0.5)	1 (<0.1)	28 (0.7)	0	49 (1.2)	1 (<0.1)
Grade 4	0	0	0	0	0	0
Missing	4 (<0.1)	6 (0.2)	74 (1.8)	12 (0.3)	2 (<0.1)	5 (0.1)
Redness	**281 (6.8)**	**107 (2.9)**	**633 (15.3)**	**77 (2.1)**	**815 (19.7)**	**167 (4.5)**
Grade 1	238 (5.8)	101 (2.7)	446 (10.8)	75 (2.0)	596 (14.4)	159 (4.3)
Grade 2	36 (0.9)	5 (0.1)	145 (3.5)	1 (<0.1)	172 (4.2)	6 (0.2)
Grade 3	7 (0.2)	1 (<0.1)	42 (1.0)	1 (<0.1)	47 (1.1)	2 (<0.1)
Grade 4	0	0	0	0	0	0
Missing	6 (0.1)	8 (0.2)	76 (1.8)	13 (0.4)	3 (<0.1)	5 (0.1)
Swelling	**774 (18.7)**	**108 (2.9)**	**1241 (30.0)**	**113 (3.1)**	**1548 (37.4)**	**200 (5.4)**
Grade 1	660 (16.0)	100 (2.7)	974 (23.5)	110 (3.0)	1211 (29.3)	189 (5.1)
Grade 2	102 (2.5)	7 (0.2)	240 (5.8)	3 (<0.1)	300 (7.3)	10 (0.3)
Grade 3	12 (0.3)	1 (<0.1)	27 (0.7)	0	37 (0.9)	1 (<0.1)
Grade 4	0	0	0	0	0	0
Missing	5 (0.1)	6 (0.2)	74 (1.8)	12 (0.3)	2 (<0.1)	5 (0.1)

Supplementary Table S10 | Incidence of Solicited Systemic Adverse Events (SAS)

'N' is the total number of participants in the Safety Analysis Set (SAS) who received a given vaccination. 'n' is the number of a participants reporting at least 1 occurrence of the specified event category and is shown as a percentage in brackets. For each category, Grade 1 = Mild; Grade 2 = Moderate; Grade 3 = Severe; Grade 4 = Potentially life threatening. If a participant had the same AE but with different grades over time, the highest grade was reported. 'Missing' rows counted participants within the population if they did not have a non-missing assessment or had an assessment with a non-graded value. Medically implausible fever temperature values were excluded from table.

n (%)	Vaccination 1		Vaccination 2		Overall	
	CoVLP+ AS03	Placebo	CoVLP+ AS03	Placebo	CoVLP+ AS03	Placebo
	N = 4 136	N = 3 683	N = 4 136	N = 3 683	N = 4 136	N = 3 683
≥1 solicited systemic AE	**2835 (68.5)**	**2023 (54.9)**	**3190 (77.1)**	**1517 (41.2)**	**3612 (87.3)**	**2394 (65.0)**
Grade 1	2017 (48.8)	1602 (43.5)	1388 (33.6)	1147 (31.1)	1538 (37.2)	1734 (47.1)
Grade 2	776 (18.8)	397 (10.8)	1671 (40.4)	349 (9.5)	1906 (46.1)	617 (16.8)
Grade 3	42 (1.0)	24 (0.7)	129 (3.1)	20 (0.5)	166 (4.0)	42 (1.1)
Grade 4	0	0	2 (<0.1)	1 (<0.1)	2 (<0.1)	1 (<0.1)
Missing	2 (<0.1)	6 (0.2)	72 (1.7)	12 (0.3)	2 (<0.1)	5 (0.1)
Chills	**571 (13.8)**	**352 (9.6)**	**1693 (40.9)**	**263 (7.1)**	**1889 (45.7)**	**522 (14.2)**
Grade 1	469 (11.3)	314 (8.5)	966 (23.4)	228 (6.2)	1 108 (26.8)	451 (12.2)
Grade 2	98 (2.4)	38 (1.0)	702 (17.0)	34 (0.9)	753 (18.2)	70 (1.9)
Grade 3	4 (<0.1)	0	24 (0.6)	1 (<0.1)	27 (0.7)	1 (<0.1)
Grade 4	0	0	1 (<0.1)	0	1 (<0.1)	0
Missing	8 (0.2)	9 (0.2)	74 (1.8)	12 (0.3)	2 (<0.1)	5 (0.1)
Fatigue	**1490 (36.0)**	**1038 (28.2)**	**2277 (55.1)**	**792 (21.5)**	**2634 (63.7)**	**1352 (36.7)**
Grade 1	1144 (27.7)	820 (22.3)	1270 (30.7)	638 (17.3)	1460 (35.3)	1018 (27.6)
Grade 2	332 (8.0)	206 (5.6)	942 (22.8)	142 (3.9)	1096 (26.5)	311 (8.4)
Grade 3	14 (0.3)	12 (0.3)	65 (1.6)	12 (0.3)	78 (1.9)	23 (0.6)
Grade 4	0	0	0	0	0	0
Missing	8 (0.2)	8 (0.2)	72 (1.7)	12 (0.3)	2 (<0.1)	5 (0.1)
Feeling of General Discomfort	**1200 (29.0)**	**699 (19.0)**	**2280 (55.1)**	**574 (15.6)**	**2595 (62.7)**	**1002 (27.2)**
Grade 1	907 (21.9)	582 (15.8)	1154 (27.9)	459 (12.5)	1341 (32.4)	784 (21.3)
Grade 2	278 (6.7)	111 (3.0)	1089 (26.3)	109 (3.0)	1203 (29.1)	207 (5.6)
Grade 3	15 (0.4)	6 (0.2)	36 (0.9)	6 (0.2)	50 (1.2)	11 (0.3)
Grade 4	0	0	1 (<0.1)	0	1 (<0.1)	0
Missing	8 (0.2)	9 (0.2)	74 (1.8)	13 (0.4)	2 (<0.1)	5 (0.1)

n (%)	Vaccination 1		Vaccination 2		Overall	
	CoVLP+ AS03	Placebo	CoVLP+ AS03	Placebo	CoVLP+ AS03	Placebo
	N = 4 136	N = 3 683	N = 4 136	N = 3 683	N = 4 136	N = 3 683
Feeling of Swelling in the Axilla (Armpit)	**266 (6.4)**	**123 (3.3)**	**461 (11.1)**	**71 (1.9)**	**613 (14.8)**	**182 (4.9)**
Grade 1	233 (5.6)	121 (3.3)	389 (9.4)	66 (1.8)	515 (12.5)	175 (4.8)
Grade 2	32 (0.8)	2 (<0.1)	70 (1.7)	5 (0.1)	95 (2.3)	7 (0.2)
Grade 3	1 (<0.1)	0	2 (<0.1)	0	3 (<0.1)	0
Grade 4	0	0	0	0	0	0
Missing	8 (0.2)	9 (0.2)	75 (1.8)	13 (0.4)	3 (<0.1)	5 (0.1)
Feeling of Swelling in the Neck	**475 (11.5)**	**328 (8.9)**	**632 (15.3)**	**245 (6.7)**	**905 (21.9)**	**484 (13.1)**
Grade 1	427 (10.3)	298 (8.1)	514 (12.4)	217 (5.9)	746 (18.0)	432 (11.7)
Grade 2	46 (1.1)	28 (0.8)	112 (2.7)	28 (0.8)	151 (3.7)	50 (1.4)
Grade 3	2 (<0.1)	2 (<0.1)	6 (0.1)	0	8 (0.2)	2 (<0.1)
Grade 4	0	0	0	0	0	0
Missing	8 (0.2)	9 (0.2)	75 (1.8)	13 (0.4)	3 (<0.1)	5 (0.1)
Fever	**44 (1.1)**	**34 (0.9)**	**355 (8.6)**	**18 (0.5)**	**390 (9.4)**	**52 (1.4)**
Grade 1	31 (0.7)	26 (0.7)	259 (6.3)	10 (0.3)	282 (6.8)	36 (1.0)
Grade 2	10 (0.2)	7 (0.2)	70 (1.7)	6 (0.2)	79 (1.9)	13 (0.4)
Grade 3	3 (<0.1)	1 (<0.1)	25 (0.6)	2 (<0.1)	28 (0.7)	3 (<0.1)
Grade 4	0	0	1 (<0.1)	0	1 (<0.1)	0
Missing	59 (1.4)	59 (1.6)	92 (2.2)	27 (0.7)	8 (0.2)	11 (0.3)
Headache	**1644 (39.7)**	**1299 (35.3)**	**2325 (56.2)**	**940 (25.5)**	**2786 (67.4)**	**1662 (45.1)**
Grade 1	1288 (31.1)	1089 (29.6)	1363 (33.0)	732 (19.9)	1634 (39.5)	1300 (35.3)
Grade 2	342 (8.3)	200 (5.4)	927 (22.4)	196 (5.3)	1105 (26.7)	341 (9.3)
Grade 3	14 (0.3)	10 (0.3)	34 (0.8)	11 (0.3)	46 (1.1)	20 (0.5)
Grade 4	0	0	1 (<0.1)	1 (<0.1)	1 (<0.1)	1 (<0.1)
Missing	6 (0.1)	9 (0.2)	74 (1.8)	13 (0.4)	2 (<0.1)	5 (0.1)
Joint Aches	**642 (15.5)**	**406 (11.0)**	**1 361 (32.9)**	**313 (8.5)**	**1627 (39.3)**	**595 (16.2)**
Grade 1	510 (12.3)	355 (9.6)	838 (20.3)	268 (7.3)	1028 (24.9)	502 (13.6)
Grade 2	129 (3.1)	47 (1.3)	504 (12.2)	44 (1.2)	578 (14.0)	88 (2.4)
Grade 3	3 (<0.1)	4 (0.1)	19 (0.5)	1 (<0.1)	21 (0.5)	5 (0.1)
Grade 4	0	0	0	0	0	0
Missing	8 (0.2)	8 (0.2)	72 (1.7)	12 (0.3)	2 (<0.1)	5 (0.1)
Muscle Aches	**1768 (42.7)**	**771 (20.9)**	**2273 (55.0)**	**617 (16.8)**	**2770 (67.0)**	**1083 (29.4)**
Grade 1	1437 (34.7)	698 (19.0)	1354 (32.7)	539 (14.6)	1683 (40.7)	944 (25.6)
Grade 2	318 (7.7)	71 (1.9)	875 (21.2)	73 (2.0)	1031 (24.9)	133 (3.6)
Grade 3	13 (0.3)	2 (<0.1)	43 (1.0)	5 (0.1)	55 (1.3)	6 (0.2)
Grade 4	0	0	1 (<0.1)	0	1 (<0.1)	0
Missing	7 (0.2)	8 (0.2)	72 (1.7)	12 (0.3)	2 (<0.1)	5 (0.1)

Supplementary Table S11 | Overall Summary of Unsolicited Adverse Events up to Twenty-One Days after Each Vaccine (SAS)

'N' is the total number of participants in the Safety Analysis Set (SAS) who received a given vaccination. 'n' is the number of a participants reporting at least 1 occurrence of the specified event category and is shown as a percentage in brackets. Grade 3 = Severe. Abbreviations: AE, adverse event; AESI, adverse event of special interest; CoVLP, coronavirus-like particle; MAAE, medically attended adverse event; n, number of subjects in category; pIMDs, potential immune-mediated diseases, SAE, serious adverse event; VAED, vaccine-associated enhanced disease.

n (%)	Vaccination 1		Vaccination 2		Overall	
	CoVLP+ AS03 N= 12 036	Placebo N= 12 040	CoVLP+ AS03 N= 11 312	Placebo N= 10 775	CoVLP+ AS03 N= 12 036	Placebo N= 12040
Immediate Unsolicited AEs	19 (0.2)	19 (0.2)	4 (<0.1)	7 (<0.1)	23 (0.2)	26 (0.2)
Unsolicited AEs	1 722 (14.3)	1 647 (13.7)	1 424 (12.6)	1 132 (10.5)	2 735 (22.7)	2 451 (20.4)
≥ Grade 3	39 (0.3)	38 (0.3)	30 (0.3)	30 (0.3)	69 (0.6)	65 (0.5)
SAEs	13 (0.1)	9 (<0.1)	11 (<0.1)	8 (<0.1)	24 (0.2)	16 (0.1)
Related SAEs	0	0	0	0	0	0
MAAEs	287 (2.4)	276 (2.3)	242 (2.1)	230 (2.1)	509 (4.2)	490 (4.1)
Related MAAEs	28 (0.2)	21 (0.2)	20 (0.2)	22 (0.2)	48 (0.4)	43 (0.4)
AEs Leading to Study Withdrawal	1 (<0.1)	5 (<0.1)	0	2 (<0.1)	1 (<0.1)	7 (<0.1)
AESIs Reported by the Investigator	2 (<0.1)	0	2 (<0.1)	0	4 (<0.1)	0
AESIs Identified by Data analysis						
Potential VAED	0	0	0	0	0	0
Related Potential VAED	0	0	0	0	0	0
Related Anaphylactic Reactions	0	0	0	0	0	0
pIMDs	8 (<0.1)	5 (<0.1)	7 (<0.1)	3 (<0.1)	15 (0.1)	8 (<0.1)
Related pIMDs	1 (<0.1)	0	1 (<0.1)	1 (<0.1)	2 (<0.1)	1 (<0.1)
AEs Leading to Death	0	2 (<0.1)	0	2 (<0.1)	0	4 (<0.1)

Supplementary Table S12 | Overall Summary of Unsolicited Adverse Events from Day 43 to 201 (SAS)

'N' is the total number of participants in the Safety Analysis Set (SAS) who received a given vaccination. 'n' is the number of a participants reporting at least 1 occurrence of the specified event category and is shown as a percentage in brackets. Grade 3 = Severe. Abbreviations: AE, adverse event; AESI, adverse event of special interest; CoVLP, coronavirus-like particle; MAAE, medically attended adverse event; n, number of subjects in category; pIMDs, potential immune-mediated diseases, SAE, serious adverse event; VAED, vaccine-associated enhanced disease.

n (%)	Vaccination 1		Vaccination 2		Overall	
	CoVLP+ AS03 N= 12 036	Placebo N= 12 040	CoVLP+ AS03 N= 11 312	Placebo N= 10 775	CoVLP+ AS03 N= 12 036	Placebo N= 12040
Unsolicited AEs	1 (<0.1)	5 (<0.1)	510 (4.5)	475 (4.4)	511 (4.2)	480 (4.0)
≥ Grade 3	0	1 (<0.1)	21 (0.2)	28 (0.3)	21 (0.2)	29 (0.2)
SAEs	0	2 (<0.1)	19 (0.2)	20 (0.2)	19 (0.2)	22 (0.2)
Related SAEs	0	0	0	1 (<0.1)	0	1 (<0.1)
MAAEs	1 (<0.1)	3 (<0.1)	199 (1.8)	197 (1.8)	200 (1.7)	200 (1.7)
Related MAAEs	0	0	2 (<0.1)	2 (<0.1)	2 (<0.1)	2 (<0.1)
AEs Leading to Study Withdrawal	1 (<0.1)	0	3 (<0.1)	5 (<0.1)	4 (<0.1)	5 (<0.1)
AESIs Reported by the Investigator	0	0	2 (<0.1)	0	2 (<0.1)	0
AESIs Identified by Data analysis						
Potential VAED	0	0	0	0	0	0
Related Potential VAED	0	0	0	0	0	0
Related Anaphylactic Reactions	0	0	0	0	0	0
pIMDs	0	0	6 (<0.1)	2 (<0.1)	6 (<0.1)	2 (<0.1)
Related pIMDs	0	0	0	0	0	0
AEs Leading to Death	0	0	4 (<0.1)	5 (<0.1)	4 (<0.1)	5 (<0.1)

Supplementary Table S13 | Incidence of Specific Unsolicited Adverse Events reported up to the Safety Data cut-off date of October 25, 2021 (SAS)

'N' is the total number of participants in the Safety Analysis Set (SAS) who received a given vaccination. 'n' is the number of a participants reporting at least 1 occurrence of the specified event preferred term (PT) category and is shown as a percentage in brackets. All event PTs reported in ≥1% of subjects after receiving first and or second treatment in CoVLP+AS03 treatment group are listed.

n (%)	Vaccination 1		Vaccination 2		Overall	
	CoVLP+ AS03 N= 12036	Placebo N= 12040	CoVLP+ AS03 N= 11312	Placebo N= 10775	CoVLP+ AS03 N= 12036	Placebo N= 12040
Subjects with ≥1 unsolicited AE	**1 722 (14.3)**	**1 647 (13.7)**	**1 424 (12.6)**	**1 132 (10.5)**	**2 735 (22.7)**	**2 451 (20.4)**
Influenza	43 (0.4)	61 (0.5)	110 (1.0)	88 (0.8)	152 (1.3)	149 (1.2)
Headache	268 (2.2)	268 (2.2)	165 (1.5)	165 (1.5)	410 (3.4)	405 (3.4)
Nasal congestion	115 (1.0)	131 (1.1)	111 (1.0)	110 (1.0)	215 (1.8)	223 (1.9)
Oropharyngeal pain	76 (0.6)	90 (0.7)	75 (0.7)	82 (0.8)	147 (1.2)	169 (1.4)
Cough	57 (0.5)	73 (0.6)	60 (0.5)	57 (0.5)	115 (1.0)	127 (1.1)
Diarrhea	61 (0.5)	61 (0.5)	72 (0.6)	54 (0.5)	129 (1.1)	110 (0.9)
Nausea	61 (0.5)	45 (0.4)	74 (0.7)	42 (0.4)	128 (1.1)	85 (0.7)
Myalgia	90 (0.7)	67 (0.6)	62 (0.5)	43 (0.4)	146 (1.2)	109 (0.9)

Supplementary Table S14 | Incidence of Adverse Events of Special Interest based on Serious Adverse Events Reported after Vaccination with Other COVID-19 Vaccines (SAS)

'N' is the total number of participants in the Safety Analysis Set (SAS) who received a given vaccination. 'n' is the number of a participants reporting at least 1 occurrence of the specified event category and is shown as a percentage in brackets.

n (%)	Vaccination 1		Vaccination 2		Overall	
	CoVLP+ AS03	Placebo	CoVLP+ AS03	Placebo	CoVLP+ AS03	Placebo
	N= 12036	N= 12040	N= 11312	N= 10775	N= 12036	N= 12040
Acute respiratory distress syndrome	0	1 (<0.1)	0	0	0	1 (<0.1)
Arrhythmia	1 (<0.1)	1 (<0.1)	0	1 (<0.1)	1 (<0.1)	2 (<0.1)
Myocarditis	0	0	1 (<0.1)	1 (<0.1)	1 (<0.1)	1 (<0.1)
Pericarditis	0	0	0	0	0	0
Bell's palsy	1 (<0.1)	0	1 (<0.1)	0	2 (<0.1)	0
Facial Paralysis	0	0	1 (<0.1)	1 (<0.1)	1 (<0.1)	1 (<0.1)
Deep vein thrombosis	0	0	1 (<0.1)	0	1 (<0.1)	0
Embolism	0	0	0	0	0	0
Cerebral venous sinus thrombosis	0	0	0	0	0	0
Thrombocytopenia	0	0	0	0	0	0
Disseminated intravascular coagulation	0	0	0	0	0	0
Guillain-Barré syndrome	0	0	0	0	0	0

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