Supplementary material

Table S1-1. Summary of solicited systemic adverse events after each dosing

Time point, Severity	n (%)		
	MVC-COV1901 N=520	**AZD-1222 N=510**	**Total N=1030**
Any Solicited Systemic AEs			
After Any Dose, All severity	225 (49.0%)	297 (58.2%)	552 (53.6%)
After First Dose, All severity	216 (41.5%)	264 (51.8%)	480 (46.6%)
After Second Dose, All severity	116 (24.9%)	106 (23.1%)	222 (24.0%)
Myalgia			
After Any Dose, All severity	**117 (22.5%)**	**167 (32.7%)**	**284 (27.6%)**
Grade 1	110 (21.2%)	152 (29.8%)	262 (25.4%)
Grade 2	21 (4.0%)	40 (7.8%)	61 (5.9%)
Grade 3	6 (1.2%)	4 (0.8%)	10 (1.0%)
After First Dose, All severity	**86 (16.5%)**	**150 (29.4%)**	**236 (22.9%)**
Grade 1	79 (15.2%)	132 (25.9%)	211 (20.5%)
Grade 2	13 (2.5%)	37 (7.3%)	50 (4.9%)
Grade 3	1 (0.2%)	4 (0.8%)	5 (0.5%)
After Second Dose, All severity	**52 (11.2%)**	**39 (8.5%)**	**91 (9.8%)**
Grade 1	47 (10.1%)	34 (7.4%)	81 (8.8%)
Grade 2	10 (2.1%)	7 (1.5%)	17 (1.8%)
Grade 3	5 (1.1%)	0 (0.0%)	5 (0.5%)
Malaise/Fatigue			
After Any Dose, All severity	**107 (20.6%)**	**141 (27.6%)**	**248 (24.1%)**
Grade 1	101 (19.4%)	126 (24.7%)	227 (22.0%)
Grade 2	3 (0.6%)	5 (1.0%)	8 (0.8%)
Grade 3	3 (0.6%)	5 (1.0%)	8 (0.8%)
Grade 4	0 (0.0%)	1 (0.2%)	1 (0.1%)
After First Dose, All severity	**75 (14.4%)**	**115 (22.5%)**	**190 (18.4%)**
Grade 1	71 (13.7%)	99 (19.4%)	170 (16.5%)
Grade 2	15 (2.9%)	28 (5.5%)	43 (4.2%)
Grade 3	2 (0.4%)	2 (0.4%)	4 (0.4%)
Grade 4	0 (0.0%)	1 (0.2%)	1 (0.1%)
After Second Dose, All severity	**53 (11.4%)**	**45 (9.8%)**	**98 (10.6%)**
Grade 1	50 (10.7%)	41 (8.9%)	91 (9.8%)
Grade 2	12 (2.6%)	7 (1.5%)	19 (2.1%)
Grade 3	1 (0.2%)	3 (0.7%)	4 (0.4%)
Headache			

Time point, Severity	n (%)		
	MVC-COV1901 N=520	AZD-1222 N=510	Total N=1030
After Any Dose, All severity	**146 (28.1%)**	**192 (37.6%)**	**338 (32.8%)**
Grade 1	136 (26.2%)	166 (32.5%)	302 (29.3%)
Grade 2	31 (6.0%)	45 (8.8%)	76 (7.4%)
Grade 3	5 (1.0%)	10 (2.0%)	15 (1.5%)
After First Dose, All severity	**116 (22.3%)**	**165 (32.4%)**	**281 (27.3%)**
Grade 1	106 (20.4%)	142 (27.8%)	248 (24.1%)
Grade 2	21 (4.0%)	36 (7.1%)	57 (5.5%)
Grade 3	2 (0.4%)	10 (2.0%)	12 (1.2%)
After Second Dose, All severity	**60 (12.9%)**	**59 (12.9%)**	**119 (12.9%)**
Grade 1	53 (11.4%)	53 (11.5%)	106 (11.5%)
Grade 2	14 (3.0%)	9 (2.0%)	23 (2.5%)
Grade 3	3 (0.6%)	1 (0.2%)	4 (0.4%)
Fever			
After Any Dose, All severity	**54 (10.4%)**	**97 (19.0%)**	**151 (14.7%)**
Grade 1	33 (6.3%)	73 (14.3%)	106 (10.3%)
Grade 3	21 (4.0%)	31 (6.1%)	52 (5.0%)
After First Dose, All severity	**35 (6.7%)**	**86 (16.9%)**	**121 (11.7%)**
Grade 1	24 (4.6%)	65 (12.7%)	89 (8.6%)
Grade 3	11 (2.1%)	23 (4.5%)	34 (3.3%)
After Second Dose, All severity	**22 (4.7%)**	**20 (4.4%)**	**42 (4.5%)**
Grade 1	12 (2.6%)	14 (3.1%)	26 (2.8%)
Grade 3	10 (2.1%)	8 (1.7%)	18 (1.9%)
Chills			
After Any Dose, All severity	**40 (7.7%)**	**77 (15.1%)**	**117 (11.4%)**
Grade 1	38 (7.3%)	67 (13.1%)	105 (10.2%)
Grade 2	8 (1.5%)	12 (2.4%)	20 (1.9%)
Grade 3	2 (0.4%)	3 (0.6%)	5 (0.5%)
Grade 4	0 (0.0%)	1 (0.2%)	1 (0.1%)
After First Dose, All severity	**25 (4.8%)**	**68 (13.3%)**	**93 (9.0%)**
Grade 1	24 (4.6%)	59 (11.6%)	83 (8.1%)
Grade 2	6 (1.2%)	10 (2.0%)	16 (1.6%)
Grade 3	0 (0.0%)	3 (0.6%)	3 (0.3%)
Grade 4	0 (0.0%)	1 (0.2%)	1 (0.1%)
After Second Dose, All severity	**21 (4.5%)**	**15 (3.3%)**	**36 (3.9%)**
Grade 1	19 (4.1%)	14 (3.1%)	33 (3.6%)
Grade 2	3 (0.6%)	2 (0.4%)	5 (0.5%)

Time point, Severity	n (%)		
	MVC-COV1901 N=520	**AZD-1222 N=510**	**Total N=1030**
Grade 3	2 (0.4%)	0 (0.0%)	2 (0.2%)
Joint Pain			
After Any Dose, All severity	**59 (11.3%)**	**93 (18.2%)**	**152 (14.8%)**
Grade 1	53 (10.2%)	87 (17.1%)	140 (13.6%)
Grade 2	12 (2.3%)	20 (3.9%)	32 (3.1%)
Grade 3	2 (0.4%)	3 (0.6%)	5 (0.5%)
Grade 4	0 (0.0%)	1 (0.2%)	1 (0.1%)
After First Dose, All severity	**41 (7.9%)**	**78 (15.3%)**	**119 (11.6%)**
Grade 1	40 (7.7%)	71 (13.9%)	111 (10.8%)
Grade 2	3 (0.6%)	16 (3.1%)	19 (1.8%)
Grade 3	1 (0.2%)	3 (0.6%)	4 (0.4%)
Grade 4	0 (0.0%)	1 (0.2%)	1 (0.1%)
After Second Dose, All severity	**23 (4.9%)**	**24 (5.2%)**	**47 (5.1%)**
Grade 1	15 (3.2%)	22 (4.8%)	37 (4.0%)
Grade 2	10 (2.1%)	5 (1.1%)	15 (1.6%)
Grade 3	1 (0.2%)	0 (0.0%)	1 (0.1%)
Diarrhea			
After Any Dose, All severity	**39 (7.5%)**	**44 (8.6%)**	**83 (8.1%)**
After First Dose, All severity	**26 (5.0%)**	**29 (5.7%)**	**55 (5.3%)**
After Second Dose, All severity	**14 (3.0%)**	**16 (3.5%)**	**30 (3.2%)**
Nausea			
After Any Dose, All severity	**60 (11.5%)**	**51 (10.0%)**	**111 (10.8%)**
After First Dose, All severity	**44 (8.5%)**	**41 (8.0%)**	**85 (8.3%)**
After Second Dose, All severity	**19 (4.1%)**	**16 (3.5%)**	**35 (3.8%)**

Table S1-2. Summary of solicited local adverse events after each dosing

Time point, Severity	n (%)		
	MVC-COV1901 N=520	**AZD-1222 N=510**	**Total N=1030**
Any Solicited Local AEs			
After Any Dose, All severity	209 (40.2%)	256 (50.2%)	465 (45.1%)
After First Dose, All severity	140 (26.9%)	202 (39.6%)	342 (33.2%)
After Second Dose, All severity	123 (26.4%)	116 (25.3%)	239 (25.8%)
Pain/Tenderness			
After Any Dose, All severity	**173 (33.3%)**	**215 (42.2%)**	**388 (37.7%)**
Grade 1	166 (31.9%)	205 (40.2%)	371 (36.0%)
Grade 2	22 (4.2%)	42 (8.2%)	64 (6.2%)
Grade 3	5 (1.0%)	7 (1.4%)	12 (1.2%)
Grade 4	0 (0.0%)	1 (0.2%)	1 (0.1%)
After First Dose, All severity	**105 (20.2%)**	**169 (33.1%)**	**274 (26.6%)**
Grade 1	96 (18.5%)	158 (31.0%)	254 (24.7%)
Grade 2	19 (3.7%)	33 (6.5%)	52 (5.0%)
Grade 3	0 (0.0%)	6 (1.2%)	6 (0.6%)
Grade 4	0 (0.0%)	1 (0.2%)	1 (0.1%)
After Second Dose, All severity	**100 (21.5%)**	**92 (20.0%)**	**192 (20.8%)**
Grade 1	95 (20.4%)	86 (18.7%)	181 (19.6%)
Grade 2	8 (1.7%)	10 (2.2%)	18 (1.9%)
Grade 3	5 (1.1%)	1 (0.2%)	6 (0.6%)
Injection site pruritus			
After Any Dose, All severity	**73 (14.0%)**	**81 (15.9%)**	**154 (15.0%)**
Grade 1	67 (12.9%)	78 (15.3%)	145 (14.1%)
Grade 2	9 (1.7%)	5 (1.0%)	14 (1.4%)
Grade 3	1 (0.2%)	1 (0.2%)	2 (0.2%)
Grade 4	0 (0.0%)	1 (0.2%)	1 (0.1%)
After First Dose, All severity	**60 (11.5%)**	**71 (13.9%)**	**131 (12.7%)**
Grade 1	54 (10.4%)	68 (13.3%)	122 (11.8%)
Grade 2	9 (1.7%)	4 (0.8%)	13 (1.3%)
Grade 3	1 (0.2%)	1 (0.2%)	2 (0.2%)
Grade 4	0 (0.0%)	1 (0.2%)	1 (0.1%)
After Second Dose, All severity	**31 (6.7%)**	**19 (4.1%)**	**50 (5.4%)**
Grade 1	31 (6.7%)	19 (4.1%)	50 (5.4%)
Grade 2	0 (0.0%)	1 (0.2%)	1 (0.1%)
Erythema/Redness			
After Any Dose, All severity	**10 (1.9%)**	**22 (4.3%)**	**32 (3.1%)**
Grade 1	8 (1.5%)	18 (3.5%)	26 (2.5%)
Grade 2	2 (0.4%)	5 (1.0%)	7 (0.7%)
After First Dose, All severity	**4 (0.8%)**	**14 (2.7%)**	**18 (1.7%)**
Grade 1	3 (0.6%)	13 (2.5%)	16 (1.6%)

Time point, Severity	n (%)		
	MVC-COV1901 N=520	**AZD-1222 N=510**	**Total N=1030**
Grade 2	1 (0.2%)	3 (0.4%)	3 (0.3%)
After Second Dose, All severity	**6 (1.3%)**	**8 (1.7%)**	**14 (1.5%)**
Grade 1	5 (1.1%)	5 (1.1%)	10 (1.1%)
Grade 2	1 (0.2%)	3 (0.7%)	4 (0.4%)
Induration/Swelling			
After Any Dose, All severity	**10 (2.0%)**	**13 (2.5%)**	**23 (2.2%)**
Grade 1	8 (1.5%)	11 (2.2%)	19 (1.8%)
Grade 2	2 (0.4%)	3 (0.6%)	5 (0.5%)
After First Dose, All severity	**7 (1.4%)**	**9 (1.8%)**	**16 (1.6%)**
Grade 1	6 (1.2%)	8 (1.6%)	14 (1.4%)
Grade 2	1 (0.2%)	1 (0.2%)	2 (0.2%)
After Second Dose, All severity	**3 (0.6%)**	**5 (1.0%)**	**8 (0.8%)**
Grade 1	2 (0.4%)	3 (0.6%)	5 (0.5%)
Grade 2	1 (0.2%)	2 (0.4%)	3 (0.3%)
Hematoma			
After Any Dose, All severity	**42 (8.1%)**	**43 (8.4%)**	**85 (8.3%)**
Grade 2	29 (5.6%)	32 (6.3%)	61 (5.9%)
Grade 3	13 (2.5%)	12 (2.4%)	25 (2.4%)
After First Dose, All severity	**33 (6.3%)**	**32 (6.3%)**	**65 (6.3%)**
Grade 2	24 (4.6%)	22 (4.3%)	46 (4.5%)
Grade 3	9 (1.7%)	11 (2.2%)	20 (1.9%)
After Second Dose, All severity	**14 (3.0%)**	**12 (2.6%)**	**26 (2.8%)**
Grade 2	10 (2.1%)	11 (2.4%)	21 (2.3%)
Grade 3	4 (0.9%)	1 (0.2%)	5 (0.5%)

Table S2. Summary of unsolicited and other adverse events

	MVC-COV1901 N=520		AZD-1222 N=510		Total N=1030	
	E	**n (%)**	**E**	**n (%)**	**E**	**n (%)**
Unsolicited AEs	11	8 (1.5)	9	8 (1.6)	20	16 (1.6)
Unsolicited AEs ≥ Grade 3	2	2 (0.4)	1	1 (0.2)	3	3 (0.3)
SAEs	2	2 (0.4)	1	1 (0.2)	3	3 (0.3)
Related SAEs	0	0	0	0	0	0
AEs ≥ Grade 3	73	50 (9.6)	95	69 (13.5)	168	119 (11.6)
AESI	1	1 (0.2)	0	0	1	1 (0.1)
VAED	0	0	0	0	0	0
AEs leading to study intervention discontinuation	2	2 (0.4)	1	1 (0.2)	3	3 (0.3)
AEs leading to study withdrawal	0	0	0	0	0	0
Death	0	0	0	0	0	0

Abbreviation: E=no. of events, AE=adverse event, SAE= serious adverse event, AESI=adverse events of special interest, VAED= vaccine-associated enhanced disease

Note: % = percentage of participants with N as the denominator; participants might be counted in more than one category; exact 95% CIs are presented.

1. Table S3. Geometric Mean Titers and Geometric Mean Titer Ratio of neutralizing antibodies (in IU/mL)

Parameter	Vaccine		GMT ratio[1] (95% CI)	p-value[2]
	AZD1222	MVC-COV1901		
Seropositive				
n	70	72		
Baseline				
GMT 95%CI	76.4 59.9-97.4	73.2 57.6-93.1		
Day 14 after 2nd shot				
GMT 95%CI	1143.4 895.3-1460.2	1905.6 1617.98-2244.3	1.7 (1.2-2.2)	<0.001
GMFR 95% CI	14.97 10.6-21.1	26.02 19.5-34.7		
Seronegative				
n	39	44		
Baseline				
GMT 95%CI	5.04 5.04-5.04	5.04 5.04-5.04		
Day 14 after 2nd shot				
GMT 95%CI	90.4 61.1-133.9	434.6 333.4-566.5	4.8 (3.01-7.7)	<0.0001
GMFR 95% CI	17.9 12.2-26.4	86.2 66.4-111.9		

Abbreviation: n= no. of participants, CI= confidence interval, GMT= geometric mean titer, GMFR= geometric mean fold rise

Note: [1] GMT ratio was computed as, $GMT_{MVC\text{-}COV1901}/GMT_{AZD1222}$

[2] p-value based on two-sample t test or Wilcoxon rank sum test

Clinical study protocol

A Phase III, Parallel Group, Prospective, Randomized, Double-blind, Active-controlled, Two-arm, Multi-center Study to Evaluate the Immunogenicity, Safety, and Tolerability of the SARS-CoV-2 Vaccine Candidate MVC-COV1901 Compared to AZD1222 Vaccine in Adult Volunteers of 18 Years and Above

Protocol Number:	CT-COV-31
Amendment Number:	Not applicable
Test Product:	MVC-COV1901
Control Product:	AZD1222
Study Phase:	III
Sponsor Name:	Medigen Vaccine Biologics Corporation
Legal Registered Address:	7F., No.16, Lane 120, Sec.1, Neihu Rd., Neihu Dist., Taipei City 114, Taiwan.
Regulatory Agency Identifier Number(s):	ClinicalTrials.gov: NCT05011526 IND number: N/A EudraCT number: N/A
Protocol Version and Date:	Version 2.0, 22-Feb-2022.
Brief Title:	A Phase III study to evaluate immunogenicity and safety with MVC-COV1901 vaccine compared with AZD1222 in participants aged 18 years and above

Document History

Document	Protocol version	Date
Amendment 2	*version 2.0*	*22-Feb-2022*
Amendment 1	*version 1.1*	*26-Nov-2021*
Original Protocol	*version 1.0*	*06-Aug-2021*

Protocol Approval Signature Page

Protocol Title:	A Phase III, Parallel Group, Prospective, Randomized, Double-blind, Active-controlled, Two-arm, Multi-center Study to Evaluate the Immunogenicity, Safety, and Tolerability of the SARS-CoV-2 Vaccine Candidate MVC-COV1901 Compared to AZD1222 Vaccine in Adult Volunteers of 18 Years and Above
Protocol Number:	CT-COV-31
Protocol Version and Date	Version 2.0, 22-Feb-2022

I have read and understand the contents of this clinical protocol and agree to meet all obligations as detailed in all applicable regulations and guidelines. In addition, I will inform the Principal Investigator and all other Investigators of all relevant information that becomes available during the conduct of this study.

This study will be conducted in compliance with the clinical study protocol (and amendments), The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for current Good Clinical Practice (GCP) and applicable regulatory requirements.

Sponsor Signatory

[redacted], MD

Medical Affairs Associate Director

Signature

Date

Medigen Vaccine Biologics Corporation
7F., No.16, Lane 120, Sec.1,
Neihu Rd., Neihu Dist.,
Taipei City 114, Taiwan.

Statement of Compliance

Protocol Title:	A Phase III, Parallel Group, Prospective, Randomized, Double-blind, Active-controlled, Two-arm, Multi-center Study to Evaluate the Immunogenicity, Safety, and Tolerability of the SARS-CoV-2 Vaccine Candidate MVC-COV1901 Compared to AZD1222 Vaccine in Adult Volunteers of 18 Years and Above
Protocol Number:	CT-COV-31
Protocol Version and Date	Version 2.0, 22-Feb-2022

The signature below constitutes the approval of this protocol and the attachments and assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and ICH guidelines. No deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB) or Independent Ethics Committee (IEC), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

Principal Investigator:

Affiliation:

_____
Signature

Address:

_____
Date

Phone

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title:

A Phase III, Parallel Group, Prospective, Randomized, Double-blind, Active-controlled, Two-arm, Multi-center Study to Evaluate the Immunogenicity, Safety, and Tolerability of the SARS-CoV-2 Vaccine Candidate MVC-COV1901 Compared to AZD1222 Vaccine in Adult Volunteers of 18 Years and Above

Brief Title:

A Phase III study to evaluate immunogenicity and safety of MVC-COV1901 vaccine compared with AZD1222 vaccine in participants aged 18 years and above

Rationale:

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a worldwide outbreak of a pneumonia-like respiratory disease called the coronavirus disease 2019 (COVID-19) since it was first reported in Wuhan, Hubei Province, China in December 2019. There is a critical unmet need for prophylactic measures to effectively contain the spread of SARS-CoV-2 infection worldwide. There remain gaps in the vaccination coverage for the global population despite the roll-out of a number of COVID-19 vaccines. The availability of more COVID-19 vaccines which are safe and effective represents the most important approach to ensure equitable access to vaccine, increase vaccination coverage, and accelerate mass immunization globally.

MVC-COV1901 is a protein-based subunit vaccine comprising S-2P protein, a modified form of the spike (S) protein of SARS-CoV-2, that is being investigated for the prevention of COVID-19 in adult participants. MVC-COV1901 is formulated to contain cytosine phosphoguanine (CpG) 1018 and aluminum hydroxide ($Al[OH]_3$) as adjuvants which enhance recognition by the innate immune system. Cumulative clinical data of MVC-COV1901 showed that it is safe and well tolerated, as well as able to induce robust immune responses compared to placebo.

This Phase III study evaluates the immunogenicity, safety, and tolerability of 15 μg MVC-COV1901 compared to the approved AZD1222 from AstraZeneca/Oxford University as the active control.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Primary Immunogenicity	
To demonstrate the immunogenic superiority of MVC-COV1901 to AZD1222 in terms of neutralizing antibody titers at 14 days after the second dose of study intervention on the first 225 evaluable subjects.	Geometric mean titers (GMT) ratio of anti-SARS-CoV-2 neutralizing antibody at 14 days after the second dose of study intervention (Visit 4/Day 43). - Superiority of MVC-COV1901 to AZD1222 in GMT of neutralizing antibody is established when the lower limit of two-sided 95% Confidence Interval (CI) of the ratio of $GMT_{MVC\text{-}COV1901}/GMT_{AZD1222} > 1$.
To demonstrate the immunogenic non-inferiority of MVC-COV1901 to AZD1222 in Seroconversion rate (SCR) of neutralizing antibody titers at 14 days after the second dose of study intervention.	SCR of anti-SARS-CoV-2 neutralizing antibody at 14 days after the second dose of study intervention (Visit 4/Day 43). Note: - Seroconversion is defined as at least 4-fold increase of post-study intervention antibody titers from the baseline titer or from half of the lower limit of detection (LoD) if undetectable at baseline - Non-inferiority of MVC-COV1901 to AZD1222 in SCR of neutralizing antibody is established when the lower limit of two-sided 95% CI of the difference $SCR_{MVC\text{-}COV1901}\text{-}SCR_{AZD1222} \geq -5\%$.
Primary Safety	
To evaluate the safety and tolerability of MVC-COV1901 compared to AZD1222 from Visit 2/Day 1 to Visit 5/Day 57 (28 days after the second dose of study intervention)	The number and percentage of participants with the occurrence of: • Solicited local adverse events (AEs) (up to 7 days after each dose of study intervention), including pain/tenderness, erythema/redness, induration/swelling, bruising and pruritus • Solicited systemic AEs (up to 7 days after each dose of study intervention), including fever, malaise/fatigue, myalgia, headache, nausea/vomiting, diarrhea, chillness, and joint pain • Unsolicited AEs (up to 28 days after each dose of study intervention) • Medically attended AEs (MAAEs) • AEs of special interest (AESIs) • Vaccine-associated enhanced disease (VAED) • Serious adverse events (SAEs)

Secondary Immunogenicity	
To evaluate the immunogenicity of MVC-COV1901 compared to AZD1222 in terms of antigen-specific immunoglobulin titers	Anti-SARS-CoV-2 antigen-specific immunoglobulin titers from Visit 3/Day 29 to Visit 7/Day 209 in terms of: • GMT • Seroconversion rate (SCR) (at Visit 4/ day 43) • GMT ratio Note: GMT ratio is defined as geometric mean of fold increase of post-study intervention titers over the baseline titers
Secondary Safety	
To evaluate the safety of MVC-COV1901 compared to AZD1222 over the study period	The number and percentage of participants with the occurrence of: • MAAEs • AESIs • VAED • SAEs
Exploratory	
To evaluate the immunogenicity of MVC-COV1901 compared to AZD1222 in terms of antigen-specific antibody titers	antigen-specific antibody titers from Visit 3/Day 29 to Visit 7/Day 209 in terms of: • GMT • SCR • GMT ratio
To estimate the efficacy of MVC-COV1901 compared to AZD1222 in the prevention of COVID-19	• Laboratory-confirmed COVID-19 cases incidence per 1000 person-years occurring ≥ 15 days after any dose of study intervention. • Laboratory-confirmed COVID-19 severe cases incidence per 1000 person-years occurring ≥ 15 days after any dose of study intervention.

Primary Estimand:

The primary clinical question of interest: to demonstrate immunogenic superiority of 2 doses MVC-COV1901 to 2 doses AZD1222 in terms of GMT ratio of anti-SARS-CoV-2 neutralizing antibody at 14 days after the second dose of study intervention.

The estimand is described by the following attributes:

Attribute	Description
Treatment	2 doses of 0.5 ml of MVC-COV1901 (test product) vs. 2 doses of 0.5 ml of AZD1222 (active control)
Population	Adult volunteers aged 18 years and above who are generally healthy or with stable pre-existing medical conditions, and as defined by the protocol inclusion/exclusion

Attribute	Description
	criteria. The target population excludes participants who have received investigational or approved COVID-19 vaccine and those with known SARS-CoV-2 infection within 3 months before the first dose of study intervention.
Endpoint	GMT of neutralizing antibody at 14 days after the second dose of study intervention (Visit 4/Day 43).
Intercurrent events	All intercurrent events, such as missed dose and withdrawal from the study before the timepoint of endpoint assessment, will be handled by a principal stratum strategy, or can refer to section 9.3.2.
Population-level summary	The GMT ratio and the associated two-sided 95% confidence interval (CI) of neutralizing antibody at Visit 4/Day 43 will be calculated for the study interventions to demonstrate immunogenic superiority based on the protocol-defined superiority criterion.

Overall Design:

This is a Phase III, parallel group, prospective, randomized, double-blind, active-controlled, two-arm, multi-center study to be conducted in approximately 1020 participants aged 18 years and above who are generally healthy or with stable pre-existing medical conditions. The participants, investigators, the site personnel, and the Sponsor staff who are involved in the blinded conduct of the study will be blinded to the study intervention assignment. Preparation and administration of study intervention will be performed by authorized unblinded site personnel who do not participate in the evaluation of the participants.

Eligible participants will be randomized to receive either MVC-COV1901 or AZD1222 vaccine in a 1:1 ratio. Simple random sampling will be used to select study participants by study site.

Unscheduled visit(s) may be arranged when deemed necessary by the investigator or study medical monitor.

An Independent Data Monitoring Committee (IDMC) will be established to provide oversight, to ensure safe and ethical conduct of the study.

Brief Summary:

The primary objective of the study is to measure the anti-SARS-CoV-2 neutralizing antibody titers in adult participants to demonstrate immunogenic superiority of MVC-COV1901 to the active control, AZD1222 vaccine, in terms of the GMT ratio of neutralizing antibodies at 14 days after the second dose of study intervention. This study also assesses the safety and tolerability of the study intervention and explores the immunogenicity in terms of anti-S IgG as well as the potential efficacy of MVC-COV1901 in preventing COVID-19. This study is aimed to recruit participants at approximately 2 study sites in the South American region.

Study details include:

- The study duration per participant will be approximately 237 days (28 days screening, 29 days treatment, and 180 days follow-up).
- The treatment duration will be approximately 29 days.
- The study will consist of 7 on-site visits (1 screening visit, 2 treatment visits, and 4 follow-up visits).

The study consists of 7 on-site visits:

- Day -28 to Day 1, Visit 1 (Screening)
- Day 1, Visit 2 (First dose of study intervention)
- Day 29 ± 3 days, Visit 3 (Second dose of study intervention)
- Day 43 ± 3 days, Visit 4
- Day 57 ± 3 days, Visit 5
- Day 119 ± 14 days, Visit 6
- Day 209 ± 14 days, Visit 7

Number of Participants:

Approximately 1020 participants will be enrolled to achieve at least 942 participants randomly assigned to study intervention.

Note: *Enrolled* means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process and screening.

Study Population:

Inclusion criteria

Participants are eligible to be included in the study only if all the following criteria apply:

1. Male or female participant aged 18 years and above at randomization.
2. Healthy adults or adults with pre-existing medical conditions who are in stable condition (obesity, endocrinological pathologies: diabetes, hyperthyroidism, hypothyroidism, etc., lung diseases: asthma, emphysema, pulmonary fibrosis, cystic fibrosis, chronic obstructive pulmonary disease (COPD), heart diseases: arterial hypertension (HTN), arrhythmias, heart failure (HF), etc., liver diseases, renal; neurological: angiographic cerebral vasospasm (ACV), psychiatric). A stable medical condition is defined as disease not requiring significant change in therapy or hospitalization for worsening disease 3 months before enrollment and expected to remain stable for the duration of the study.
3. Female participants:
    a. A female participant is eligible if the participant is a woman of non-childbearing potential, i.e., surgically sterilized (defined as having undergone hysterectomy and/or bilateral oophorectomy and/or bilateral salpingectomy; tubal ligation alone is not considered sufficient) or one year post-menopausal.

b. If the participant is a woman of childbearing potential, she must agree to practice sexual abstinence or agree to use medically effective contraception from 14 days before screening to 30 days following the last administration of study intervention. Highly effective methods of contraception include:
    i. Implanted hormonal methods of contraception or placement of an intrauterine device or intrauterine hormonal-releasing system
    ii. Established use of hormonal methods (injectable, pill, patch or ring) combined with barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository
    iii. Azoospermic partner (vasectomized or due to medical cause), provided the partner is the sole sexual partner of the female participant and the absence of sperm has been confirmed (from medical records/examination/history).

c. Have a negative pregnancy test

4. Participant is willing and able to comply with all required study visits and follow-up required by this protocol.
5. Participant or the participant's legal representative must understand the procedures of the study and provide written informed consent.

Exclusion criteria

Participants are excluded from the study if any of the following criteria applies:

1. Pregnant or breast feeding or have plan to become pregnant within 30 days after the last administration of study intervention.
2. Employees at the investigator's site, of the Sponsor or delegate (e.g., contract research organization) who are directly involved in the conduct of the study.

Prior/Concomitant Therapy

3. Currently receiving or received any investigational intervention within 30 days prior to the first dose of study intervention.
4. Administered any licensed live-attenuated vaccines within 28 days or other licensed non-live-attenuated vaccines within 7 days prior to the first dose of study intervention.
5. Administered any blood product or intravenous immunoglobulin administration within 12 weeks prior to the first dose of study intervention.
6. Currently receiving or anticipate to receive concomitant immunosuppressive or immune-modifying therapy (excluding inhaled, topical skin and/or eye drop-containing corticosteroids, low-dose methotrexate, or < 2 weeks of daily receipt of prednisone less than 20 mg or equivalent) within 12 weeks prior to the first dose of study intervention.
7. Currently receiving or anticipate to receive treatment with tumor necrosis factor (TNF)-α inhibitors, e.g., infliximab, adalimumab, etanercept within 12 weeks prior to the first dose of study intervention.
8. Major surgery or any radiation therapy within 12 weeks prior to the first dose of study intervention.
9. Has received any other investigational or approved COVID-19 vaccine.

Medical Conditions

10. Immunosuppressive illness or immunodeficient state, including hematologic malignancy, history of solid organ, bone marrow transplantation, or asplenia.
11. A history of malignancy with potential risk for recurrence after curative treatment, or current diagnosis of or treatment for cancer (exceptions are squamous and basal cell carcinomas of the skin and treated uterine cervical carcinoma in situ, at the discretion of the investigator).
12. Bleeding disorder considered a contraindication to intramuscular (IM) injection or phlebotomy.
13. Known SARS-CoV-2 infection in the 3 months prior to the first dose of study intervention.
14. A history of cerebral venous sinus thrombosis, heparin-induced thrombocytopenia, or antiphospholipid syndrome.
15. Participant who, in the investigator's judgement, is not in a stable condition and by participating in the study could adversely affect the safety of the participant, interfere with adherence to study requirements or evaluation of any study endpoint. This may include a participant with ongoing acute diseases, severe infections, autoimmune disease, laboratory abnormality or serious medical conditions in the following systems: cardiovascular, pulmonary, hepatic, neurologic, metabolic, renal, or psychiatric.
16. A history of hypersensitivity to any vaccine or a history of allergic disease or reactions likely to be exacerbated by any component of the MVC-COV1901 or AZD1222.
17. Body (oral, rectal, or ear) temperature ≥ 38.0°C or acute illness (not including minor illnesses such as diarrhea or mild upper respiratory tract infection at the discretion of the investigator) within 2 days before the first dose of study intervention.

Intervention Groups and Duration:

Eligible participants will be randomized to one of the following 2 treatment groups in a 1:1 ratio:

- MVC-COV1901 (test product): approximately 471 participants will receive 2 doses of MVC-COV1901 (15 μg of S-2P protein/0.5 mL/dose), each at Visit 2/Day 1 and Visit 3/Day 29 via IM injection in the deltoid region.
- AZD1222 (active control): approximately 471 participants will receive 2 doses of AZD1222 (according to the approved dose), each at Visit 2/Day 1 and Visit 3/Day 29 via IM injection in the deltoid region.

No dose modification will be allowed. Any rescheduled administration of study intervention will be arranged within the visit window.

Statistical Analysis:

For the primary immunogenicity endpoint, superiority of MVC-COV1901 to AZD1222 in terms of GMT ratio of neutralizing antibody is established when the lower bound of the two-sided 95% CI of the ratio of $GMT_{MVC\text{-}COV1901}/GMT_{AZD1222}$ is > 1.

All measured variables and derived parameters will be listed by individual participant and analyzed using descriptive statistics. Summary descriptive statistics will be provided for demographic/baseline characteristics, secondary immunogenicity, safety, exploratory immunogenicity, and efficacy variables. Continuous variables will be summarized descriptively with number of participants, mean, median, standard deviation (SD), interquartile range (IQR), range (minimum and maximum), and 95% CI of mean and median (when appropriate). Categorical variables will be summarized with number and percentage of participants.

Sensitivity analysis will be performed for the primary immunogenicity endpoint by adjusting for the covariates of site, age, comorbidity, body mass index (BMI), human immunodeficiency virus (HIV) status, and baseline serostatus of anti-SARS-CoV-2 neutralizing antibody.

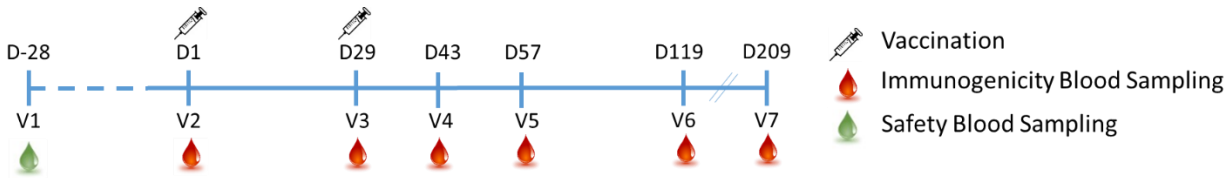
Subgroup analysis by age, comorbidity, BMI, and baseline serostatus of anti-SARS-CoV-2 neutralizing antibody will be performed for the primary immunogenicity and safety endpoints.

One interim analysis is planned in the study after all participants have completed Visit 5/Day 57 assessment.

Data Monitoring/Other Committee: Yes

An IDMC will be established for this study. The IDMC is a group of independent physicians or experts who are appointed to provide oversight, to ensure safe and ethical conduct of the study. The IDMC will evaluate cumulative SAEs and other relevant safety data monthly and make appropriate recommendations to the Sponsor based on the available data. The composition of the committee is dependent upon the medical knowledge and/or scientific skills required for monitoring the study.

1.2. Schema



1.3. Schedule of Activities (SoA)

Visit Number	1[1]	2[1]	3	4	5	6	7	ET[14]	Unscheduled[15]
Visit Day	-28 to 1	1	29 (±3)	43 (±3) (14±3 days after V3)	57 (±3) (28±3 days after V3)	119 (±14) (90±14 days after V3)	209 (±14) (180±14 days after V3)	Early Termination Visit	NA
Visit Type	Screening	Vaccination 1	Vaccination 2	Immunogenicity Visit	Immunogenicity Visit	Immunogenicity Visit	EOS	ET	NA
Procedure									
Informed consent	X								
Medical history	X	X							
Demographics	X								
Concomitant medication	X	X	X	X	X	X	X	X	
Inclusion/Exclusion criteria	X	X							
Urine or blood pregnancy test[2]	X	X	X	X	X				
Body height and weight	X								Per investigator's discretion
Physical examination[3]	X[3a]	X[3b]	X[3b]	X[3b]	X[3b]	X[3b]	X[3b]	X[3b]	
Serology test[4]	X								
Vital signs[5]	X	X	X						
Randomization		X							
Discontinuation criteria[6]		X	X	X	X	X	X	X	
Contraindication to study intervention[7]		X	X						
Blood sampling for clinical laboratory evaluation (hematology,	X								Per investigator's discretion

Visit Number	1[1]	2[1]	3	4	5	6	7	ET[14]	Unscheduled[15]
Visit Day	-28 to 1	1	29 (±3)	43 (±3) (14±3 days after V3)	57 (±3) (28±3 days after V3)	119 (±14) (90±14 days after V3)	209 (±14) (180±14 days after V3)	Early Termination Visit	NA
Visit Type	Screening	Vaccination 1	Vaccination 2	Immunogenicity Visit	Immunogenicity Visit	Immunogenicity Visit	EOS	ET	NA
Procedure									
biochemistry, immunology)[8]									
Blood sampling for immunogenicity[9]		X	X	X	X	X	X	X[14a]	
Administration of study intervention[10]		X	X						
Explanation of participant diary		X	X						
Review participant diary			X	X	X				
Solicited symptoms[11]		X	X					X[14b]	Per investigator's discretion
Unsolicited symptoms[12]		X	X	X	X			X[14c]	
MAAE, AESI, VAED, SAE		X							
Laboratory-confirmed SARS-CoV-2 infection or COVID-19 cases[13]		X							
Study completion							X		

Abbreviation: AE = adverse event; AESI = adverse events of special interest; ALT = alanine transferase; ANA = antinuclear antibody; APTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; COVID-19 = coronavirus disease 2019; Cr = creatinine; EOS = end of study; ET = early termination; Hb = hemoglobin; HbA1c = hemoglobin A1c; hCG = human chorionic gonadotropin; HIV = human immunodeficiency virus; Hct = hematocrit; MAAE = medically attended adverse event; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; NA = not applicable; RBC = red blood cell; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2; V = visit; VAED = vaccine-associated enhanced disease; WBC = white blood cell

1. Screening (Visit 1) and Vaccination 1 (Visit 2) may be performed on the same day; in this case, the assessments marked for both Visit 1 and Visit 2 will only need to be performed once.
2. Urine/blood pregnancy test (beta-hCG): for female participants with childbearing potential only.
3. Physical examination: (3a) include general appearance, skin, eyes, ears, nose, throat, head and neck, heart, chest and lungs, abdomen, extremities, lymph nodes, musculoskeletal, and neurological at screening visit; (3b) targeted examination will be performed if indicated by any change in the participant's health condition since the previous visit as determined by investigator.
   Physical examination will be performed before the administration of study intervention at Visit 2 and Visit 3.
4. Serology includes anti-HIV antibody or rapid test and anti-SARS-CoV-2 antibody rapid test.
5. Vital Signs: body temperature, pulse rate, respiratory rate, and blood pressure at sitting position. Vital signs will be performed before the administration of study intervention and approximately 30 minutes after the administration of study intervention at Visit 2 and Visit 3.
6. Discontinuation criteria: administration of prohibited medication/treatment; confirmed COVID-19 based on available medical records; any pathological event, clinical AE, or any change in the participant's condition giving an indication to the investigator that further participation in the study may not be in the best interest of the participant; pregnancy; any vaccine-related SAE during the study period.
7. Contraindication to study intervention: body (oral, rectal or ear) temperature ≥ 38.0°C or acute illness (not including minor illnesses such as diarrhea or mild upper respiratory tract infection at the discretion of the investigator) within 2 days before each administration of study intervention (the participant may be rescheduled); any non-live-attenuated vaccine within 7 days before each administration of study intervention (participant may be rescheduled); any live-attenuated vaccine within 28 days before each administration of study intervention (participant may be rescheduled); any conditions that is a contraindication to study intervention based on the judgement of the investigator.
   Note: COVID-19 vaccine other than the study intervention is prohibited throughout the study.
8. Hematology: Hb, RBC, Hct, MCV, MCH, MCHC, reticulocyte, WBC, differential of leukocytes, platelets, prothrombin time, and APTT
   Biochemistry: HbA1c, BUN, Cr, ALT, and AST
   Immunology: ANA
   Hematology, biochemistry and immunology tests at screening are to provide a reference point for evaluation of AEs during the study, if needed.
9. Blood sampling for immunogenicity will be collected for all randomized participants. Blood samples will be collected before the administration of study intervention at Visit 2 and Visit 3.
10. Before the administration of study intervention, physical examination, medical history, and pregnancy test for applicable participants, immunogenicity test, vital signs, contraindication to study intervention and elimination criteria will be assessed. At least 30 minutes after the administration of study intervention, participants will be assessed for vital signs and immediate adverse reactions.
11. Solicited AEs include administration site reactions (pain/tenderness, erythema/redness, induration/swelling, bruising and pruritus) and systemic events (fever, malaise/fatigue, myalgia, headache, nausea/vomiting, diarrhea, chillness, and joint pain) within 7 days after each administration of study intervention.
12. Unsolicited AEs are any untoward medical events other than solicited AEs which occurred within 28 days after each administration of study intervention.
13. Laboratory-confirmed cases will be collected since Day 1 of the study whenever data are available.
14. For participants who withdraw from the study before Visit 7, an early termination visit should be completed by the participants as soon as possible.
    (14a) blood samples for immunogenicity will only be taken if the early termination visit is performed at least 14 days after the previous blood sampling for immunogenicity.
    (14b) Solicited AEs will be collected if the early termination visit is performed within 7 days after the administration of study intervention.
    (14c) Unsolicited AEs will be collected if the early termination visit is performed within 28 days after the administration of study intervention.
15. Unscheduled visit will be arranged when deemed necessary by the investigator or medical monitor.

2. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a worldwide outbreak of a pneumonia-like respiratory disease called the coronavirus disease 2019 (COVID-19) since it was first reported in Wuhan, Hubei Province, China in December 2019. The virus is categorized in the betacoronavirus subfamily and it is 79% and 50% phylogenetically homological to severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), respectively (Lu et al. 2020; Coronaviridae Study Group of the International Committee on Taxonomy of Viruses). As of late June 2021, more than 180 million confirmed cases and over 3.9 million deaths due to COVID-19 have been reported globally (WHO COVID-19 Weekly Epidemiological Update). People infected with SARS-CoV-2 present with various degrees of clinical manifestation and disease severity, ranging from asymptomatic to severe or even fatal illness (WHO Living Guidance 2021).

Since the end of 2020, a number of COVID-19 vaccines which are developed by exploiting different technologies including messenger ribonucleic acid (mRNA), deoxyribonucleic acid (DNA), non-replicating viral vector, inactivated virus, and protein subunit (Rego et al. 2020; Forni and Mantovani 2021) have been approved regionally under the United States Food and Drug Administration (US FDA)'s Emergency Use Authorization (EUA) and European Medicines Agency (EMA) Conditional Marketing Authorization (CMA), as well as at the country-level. For example the mRNA vaccines from Pfizer/BioNTech and Moderna; adenovirus-based vaccines from AstraZeneca/Oxford University and Johnson & Johnson; Sputnik V and EpiVacCorona from Russia; CoronaVac and BBIBP-CorV from China; Abdala from Cuba, to name a few (FDA COVID-19 Vaccines; RAPS 2021; WHO COVID-19 Vaccine Tracker).

MVC-COV1901 is a protein-based subunit vaccine comprising S-2P protein, a modified form of the spike (S) protein of SARS-CoV-2, that is being investigated for the prevention of COVID-19 in adult participants. MVC-COV1901 is formulated to contain cytosine phosphoguanine (CpG) 1018 and aluminum hydroxide ($Al[OH]_3$) as adjuvants which enhance recognition by the innate immune system.

2.1. Study Rationale

There is a critical unmet need for prophylactic measures to effectively contain the spread of SARS-CoV-2 infection worldwide. There remain gaps in the vaccination coverage for the global population despite the roll-out of a number of COVID-19 vaccines. The availability of more COVID-19 vaccines which are safe and effective represents the most important approach to ensure equitable access to vaccine, increase vaccination coverage, and accelerate mass immunization globally.

At the time of finalizing this protocol, cumulative results from the ongoing Phase I study (NCT04487210) and Phase II study (NCT04695652) of MVC-COV1901 showed that the test product was safe and well tolerated, as well as able to induce robust immune responses compared to placebo. The current Phase III study will evaluate the immunogenicity, safety, and tolerability of MVC-COV1901 containing 15 μg of S-2P protein, adjuvanted with CpG 1018 and $Al[OH]_3$

compared to the approved AZD1222 from AstraZeneca/Oxford University as the active control. The primary objective of the study is to measure the anti-SARS-CoV-2 neutralizing antibody titers in adult participants so as to demonstrate immunogenic superiority of MVC-COV1901 to AZD1222 in terms of geometric mean titer (GMT) ratio of neutralizing antibody at 14 days after the second dose of study intervention.

2.2. Background

MVC-COV1901 is a subunit vaccine consisting of stabilized prefusion spike (S) protein ectodomain, S-2P protein encoding residues 1−1208 of SARS-CoV-2 S protein with two proline substitutions at residues 986 and 987, a "GSAS" substitution at residues 682–685 to abolish the furin cleavage site, and an insertion of T4 fibritin trimerization motif at the C-terminus. This construct conformation was shown to be able to bind angiotensin-converting enzyme 2 (ACE2) which are expressed abundantly in lung and small intestine cells (Li et al. 2003; Hamming et al. 2004) and to induce high levels of neutralizing antibody (Pallesen et al. 2017; Wrapp et al. 2020), hence inhibiting viral infection.

MVC-COV1901 is formulated with 2 adjuvants, namely CpG 1018 (a 22-mer CpG-enriched oligodeoxynucleotide [ODN] phosphorothioate) and $Al(OH)_3$. Unmethylated CpG sequences bind to toll-like receptor 9 (TLR9) on the plasmacytoid dendritic cells (pDCs) and B cells and activates the antigen presenting pDCs and B cells, thereby induces the innate and adaptive immune responses (Bode et al. 2011; Toussi et al. 2014). On the other hand, aluminum adjuvant has been widely used in preventive vaccines based on its ability to enhance antibody-mediated immune response (reviewed in Hogenesch 2013). The combination of immunostimulatory molecules with aluminum adjuvant could potentiate a cell-mediated immune response (Guy 2007; Davis et al. 1998; Cooper et al. 2004).

In nonclinical studies with mice, Kuo et al. (2020) reported that the animals injected with 1 and 5 µg of CHO cells-expressed S-2P protein combined with CpG 1018 and $Al(OH)_3$ were able to elicit neutralizing antibodies against pseudovirus, anti-S immunoglobulin G (IgG), and anti-RBD IgG at a higher level than that with CpG 1018 or $Al(OH)_3$ alone. The neutralizing activities were more pronounced after the second injection than after the first injection. Neutralizing antibodies against wild type virus were also induced at both S-2P concentration but at lower potency that that of pseudovirus. In addition, the mice immunized with S-2P combined with CpG 1018 and $Al(OH)_3$ a) produced antibodies that neutralized both pseudoviruses carrying the wild-type D614 and mutant D614G versions of spike proteins, and b) produced high level of interferon (IFN)-γ and interleukin (IL)-2 while suppressing the levels of IL-5 and IL-6, biasing towards a T helper type 1 (Th1) T cell response.

The safety of S-2P protein at 5, 25, and 50 µg, formulated with either CpG 1018 or CpG 1018 in combination with $Al(OH)_3$ was evaluated in a single-dose and a repeat-dose (2 injections on Days 1 and 15) toxicity study in rats. The results showed that S-2P protein combined with the two adjuvants administered once or twice to rats did not induce any systemic adverse effects and was considered safe and well tolerated even with an expected reaction at injection sites after dosing. Increased body temperature was observed in the animals in both single- and repeat-dose studies but it was reversible after 48 hours (Kuo et al. 2020). In a 4-week repeat-dose toxicity study, the vaccine did not induce any significant adverse effects. Abnormalities observed in the

results of the toxicity study in terms of decreased body weight, increased body temperature, abnormal clinical laboratory values, and abnormal necropsy findings were reversible during the recovery period (MVC-COV1901 Investigator Brochure).

In a virus challenge study in hamsters, the animals injected with 1 and 5 µg of S-2P protein combined with CpG 1018 and $Al(OH)_3$ first showed high levels of neutralizing antibodies and anti-spike protein immunoglobulin G (anti-S IgG) at 14 days after the second vaccination. At 4 weeks after the second vaccination, the hamsters were challenged intranasally with SARS-CoV-2 and followed up to 6 days post infection. The hamsters given both dosages did not show decreases in the body weight; no virus was detectable in the lungs of the hamsters at 3 days post infection as measured by fifty-percent tissue culture infective dose ($TCID_{50}$) and the hamsters were protected from lung injury at 6 days post infection (Lien et al. 2021).

In the clinical setting, three dose levels of S-2P protein (5, 15, and 25 µg) with CpG 1018 and $Al(OH)_3$ adjuvants were chosen for the Phase I prospective, open-label study (protocol number CT-COV-11, NCT04487210) based on the immunogenicity and toxicology profiles observed in the nonclinical studies. The study evaluated the safety and immunogenicity of 2 doses of MVC-COV1901, taken 28 apart, in 45 Taiwanese adults aged ≥ 20 to < 50 years. The results up to the data cut-off point (23-Dec-2020) showed that MVC-COV1901 was safe and well tolerated, no serious adverse event (SAE) or adverse event of special interest (AESI) occurred and all local and systemic adverse events (AEs) were mild except for one moderate malaise/fatigue in the 25 µg group. The most commonly reported local AE was pain/tenderness (80.0%), while malaise/fatigue (28.9%) was the most commonly reported systemic AEs among all treatment groups (Hsieh et al. 2021).

The GMT of live virus (wild type) and pseudovirus neutralizing antibodies, as well as anti-S IgG titers peaked at 14 days after the second dose of study intervention (Day 43). The GMT of wild type neutralizing antibody in the 5, 15, and 25 µg treatment groups on Day 43 were 0.8, 1.8, and 3.9 times the GMT of convalescent serum specimens; the GMT of pseudovirus neutralizing antibody and anti-S IgG in the 5, 15, and 25 µg treatment groups on Day 43 were 1.25 to 4.4 times and 3.3 to 5.1 times the GMT of convalescent serum specimens, respectively. The seroconversion rate was 100% in the 15 and 25 µg treatment groups after the second dose of study intervention (Hsieh et al. 2021). In terms of cellular immune response, participants in the 5, 15, and 25 µg treatment groups showed increased mean IFN-γ-secreting T cells at 161.3, 85.5, and 94.9 cells/million peripheral blood mononuclear cells, respectively, at 28 days after the second dose of study intervention; the participants also showed increased mean IL-4-secreting T cells at 24.1, 16.0, and 31.3 cells/million peripheral blood mononuclear cells, respectively, at 28 days after the second dose of study intervention (Hsieh et al. 2021). The substantially higher amount of IFN-γ- than IL-4-secreting cells suggested a Th1-skewed T cell response.

The ongoing Phase II, double-blind, randomized study (protocol number CT-COV-21, NCT04695652) is aimed to evaluate the safety, tolerability, and immunogenicity of 2 doses of 15 µg MVC-COV1901 compared to placebo, taken 28 days apart, in 3844 Taiwanese adults aged ≥ 20 years. The results up to the data cut-off point (02-Jun-2021) also showed that MVC-COV1901 was well tolerated, no study intervention-related SAEs were reported, one AESI of moderate facial paralysis was reported in the ≥ 65 years age group. Pain/tenderness

(64.4%) and malaise/fatigue (35.1%) were the most commonly reported local and systemic AE, respectively (unpublished data).

The 2-dose vaccination regimen of 15 μg MVC-COV1901 was highly immunogenic in terms of live virus (wild type) neutralizing antibodies at 28 days after second dose of study intervention (Day 57). The GMT of wild type neutralizing antibodies on Day 57 increased to 662.31 in the MVC-COV01901 group compared to 4.00 in the placebo group (P <0.0001), making the GMT ratio of the MVC-COV1901 group 163 times the GMT ratio of the placebo group (163.22 vs. 0.99). The GMT of pseudovirus neutralizing antibody and anti-S IgG peaked at 14 days after the second dose of study intervention (Day 43) and were higher in the MVC-COV1901 group than in the placebo group (P <0.0001). The seroconversion rate was 99.8% at 28 days after the second dose of study intervention (unpublished data).

A detailed description of the chemistry, pharmacology, safety, and immunogenicity of MVC-COV1901 is provided in the Investigator's Brochure.

The AZD1222 vaccine from AstraZeneca/Oxford University, used as the active control in the current study, contains the recombinant ChAdOx1-S replication-deficient chimpanzee adenovirus vector encoding the SARS-CoV-2 S glycoprotein. It is indicated for individuals ≥ 18 years of age for the prevention of COVID-19. The most frequently reported adverse reactions were injection site tenderness (63.7%), injection site pain (54.2%), headache (52.6%), fatigue (53.1%), myalgia (44.0%), malaise (44.2%), pyrexia (includes feverishness (33.6%) and fever >38°C (7.9%), chills (31.9%), arthralgia (26.4%) and nausea (21.9%). Most of the adverse reactions were mild to moderate in severity and usually resolved within a few days of vaccination. Vaccine efficacy was 62.6% (95% confidence interval [CI]: 50.9, 71.5) in participants receiving two recommended doses with any dose interval (ranging from 3 to 23 weeks) (Vaxzeria Summary of Product Characteristics).

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of MVC-COV1901 and AZD1222 may be found in the Investigator's Brochure and the summary of product characteristics, respectively.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: MVC-COV1901 and AZD1222		
Potential local injection site reactions (pain/tenderness, erythema/redness, and induration/swelling) and systemic AEs (fever,	These reactions and AEs are commonly associated with vaccines (FDA CBER Guidance 2007). Injection of aluminum adjuvants often induces a local inflammatory	Participants will be monitored for the possible AEs and/or abnormalities caused by the study intervention. All participants will be checked for

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
malaise/fatigue, myalgia, headache, nausea/vomiting, and diarrhea)	reaction such as pain, swelling, and redness at the injection site. According to the prescribing information of HEPLISAV-B® (Hepatitis B vaccine adjuvanted with 3000 mcg CpG 1018), the most common local reaction was injection site pain (23%-39%); the most common systemic reactions were fatigue (11%-17%) and headache (8%-17%). Refer to Section 2.2 for the most commonly reported local and systemic AEs of the study intervention in the clinical settings.	any contraindication to the study intervention before the administration of study intervention and will be observed for at least 30 minutes after administration of study intervention. Injections site reactions and systemic AEs will be monitored for 7 and 28 days, respectively, after each administration of study intervention.
Potential immune-mediated reactions, e.g., vaccine-associated enhanced disease (VAED), AESI, Guillain-Barré syndrome; other unknown AEs and laboratory abnormalities with a novel vaccine	For MVC-COV1901, non-clinically significant changes, considered to be related to the adjuvant, were observed in nonclinical studies in mice and rats. Up to the time of finalizing this protocol, cumulative safety results revealed no study intervention-related SAE and protocol-defined VAED occurred in the Phase I and II studies. One (< 0.1%) case of AESI (moderate facial paralysis) was reported in the Phase II study. For AZD1222, severe and very rare cases of thrombosis with thrombocytopenia syndrome have been reported post-marketing. These included venous thrombosis such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis Vaccine-associated disease enhancement has been reported for respiratory syncytial virus, feline	Participants will be monitored for the possible AEs and/or abnormalities caused by the study intervention. This study will be monitored by an Independent Data Monitoring Committee (IDMC) throughout the study to ensure the safety of the participants. Only healthy participants or those with stable pre-existing diseases/conditions will be included in the study. All participants will be checked for any contraindication to the study intervention before administration of study intervention and will be observed for at least 30 minutes after administration of study intervention. Specialized clinical management will be applied to participants diagnosed with thrombocytopenia (Vaxzeria

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	coronavirus, and Dengue virus vaccines.	Summary of Product Characteristics)
Potential allergic reaction to vaccination	Although considered rare, allergic reaction to vaccination may occur, which causes rash, urticaria, or even anaphylaxis. Up to the time of finalizing this protocol, no anaphylaxis to the use of MVC-COV1901 has been reported so far. For AZD1222, events of anaphylaxis have been reported.	The study excludes participants who have a history of hypersensitivity to vaccines or allergic reactions to the components of MVC-COV1901 and AZD1222. A second dose of the study intervention will not be given to those who have experienced anaphylaxis to the first dose.
Study Procedures		
Blood draw	The procedure of blood draw may cause pain, tenderness, bruising, bleeding, dizziness, vasovagal response, syncope, and in rare occasion, infection at the site where the blood is taken.	Only appropriately qualified personnel will perform the blood draw. Participants with bleeding disorder (which is also considered a contraindication to IM injection) will be excluded from participating in the study.
Physical attendance to healthcare facilities and exposure to SARS-CoV-2 during the pandemic	It is necessary for participants to make in-person visits to healthcare facilities for returning study visits, which increases exposure to SARS-CoV-2.	The study will follow the national guidance and local site policy in the management of the clinical study during the COVID-19 pandemic to appropriately ensure the safety of the participants.

2.3.2. Benefit Assessment

Based on the available clinical data described in Section 2.2, benefits to individual participants receiving MVC-COV1901 may include:

- Receive a potentially efficacious COVID-19 vaccine.
- Access to COVID-19 diagnostic and antibody testing.

- Contribute to the process of developing a new vaccine for COVID-19. Information obtained in this study will inform the development decisions for MVC-COV1901.

AZD1222 is an approved COVID-19 vaccine under the CMA in the European Union and at the country-level in various countries. Individual participants receiving AZD1222 will receive benefit in terms of prevention of hospitalization, intensive care unit admission, and death as a result of COVID-19 (EMA AstraZeneca's Vaccine Benefit and Risk).

2.3.3. Overall Benefit Risk Conclusion

Considering the measures taken to minimize risks to participants participating in this study, the potential risks identified in association with MVC-COV1901, AZD1222, and the study procedures are justified by the anticipated benefits that may be afforded to the participants in this study.

3. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary Immunogenicity	
To demonstrate the immunogenic superiority of MVC-COV1901 to AZD1222 in terms of neutralizing antibody titers at 14 days after the second dose of study intervention on the first 225 evaluable subjects.	GMT ratio of anti-SARS-CoV-2 neutralizing antibody at 14 days after the second dose of study intervention (Visit 4/Day 43). - Superiority of MVC-COV1901 to AZD1222 in GMT of neutralizing antibody is established when the lower limit of two-sided 95% Confidence Interval (CI) of the ratio of $GMT_{MVC\text{-}COV1901}/GMT_{AZD1222} > 1$.
To demonstrate the immunogenic non-inferiority of MVC-COV1901 to AZD1222 in Seroconversion rate (SCR) of neutralizing antibody titers at 14 days after the second dose of study intervention	SCR of anti-SARS-CoV-2 neutralizing antibody at 14 days after the second dose of study intervention (Visit 4/Day 43). Note: - Seroconversion is defined as at least 4-fold increase of post-study intervention antibody titers from the baseline titer or from half of the lower limit of detection (LoD) if undetectable at baseline - Non-inferiority of MVC-COV1901 to AZD1222 in SCR of neutralizing antibody is established when the lower limit of two-sided 95% CI of the difference $SCR_{MVC\text{-}COV1901}\text{-}SCR_{AZD1222} \geq -5\%$.
Primary Safety	
To evaluate the safety and tolerability of MVC-COV1901 compared to AZD1222 from Visit 2/Day 1 to Visit 5/Day 57 (28 days after the second dose of study intervention)	The number and percentage of participants with the occurrence of: • Solicited local AEs (up to 7 days after each dose of study intervention), including pain/tenderness, erythema/redness, induration/swelling, bruising and pruritus • Solicited systemic AEs (up to 7 days after each dose of study intervention), including fever, malaise/fatigue, myalgia, headache, nausea/vomiting, diarrhea, chillness, and joint pain • Unsolicited AEs (up to 28 days after each dose of study intervention) • Medically attended AEs (MAAEs) • AESIs • VAED • SAEs

Secondary Immunogenicity	
To evaluate the immunogenicity of MVC-COV1901 compared to AZD1222 in terms of antigen-specific immunoglobulin titers	Anti-SARS-CoV-2 *of antigen-specific immunoglobulin*titers from Visit 3/Day 29 to Visit 7/Day 209 in terms of: • GMT • Seroconversion rate (SCR) (at Visit 4/ day 43) • GMT ratio Note: GMT ratio is defined as geometric mean of fold increase of post-study intervention titers over the baseline titers
Secondary Safety	
To evaluate the safety of MVC-COV1901 compared to AZD1222 over the study period	The number and percentage of participants with the occurrence of: • MAAEs • AESIs • VAED • SAEs
Exploratory	
To evaluate the immunogenicity of MVC-COV1901 compared to AZD1222 in terms of antigen specific antibody titers	Antigen specific antibody titers from Visit 3/Day 29 to Visit 7/Day 209 in terms of: • GMT • SCR • GMT ratio
To estimate the efficacy of MVC-COV1901 compared to AZD1222 in the prevention of COVID-19	• Laboratory-confirmed COVID-19 cases incidence per 1000 person-years occurring ≥ 15 days after any dose of study intervention. • Number of laboratory-confirmed COVID-19 severe cases incidence per 1000 person-years occurring ≥ 15 days after any dose of study intervention.

Primary estimand

The primary clinical question of interest: to demonstrate immunogenic superiority of 2 doses MVC-COV1901 to 2 doses AZD1222 in terms of GMT ratio of anti-SARS-CoV-2 neutralizing antibody at 14 days after the second dose of study intervention.

The estimand is described by the following attributes:

Attribute	Description
Treatment	2 doses of MVC-COV1901 (test product) vs. 2 doses of AZD1222 (active control)
Population	Adult volunteers aged 18 years and above who are generally healthy or with stable pre-existing medical conditions, and as defined by the protocol inclusion/exclusion

Attribute	Description
	criteria. The target population excludes participants who have received investigational or approved COVID-19 vaccine and those with known SARS-CoV-2 infection within 3 months before the first dose of study intervention.
Endpoint	GMT of neutralizing antibody at 14 days after the second dose of study intervention (Visit 4/Day 43).
Intercurrent events	All intercurrent events, such as missed dose and withdrawal from the study before the timepoint of endpoint assessment, will be handled by a principal stratum strategy, or can refer to section 9.3.2.
Population-level summary	The GMT ratio and the associated two-sided 95% CI of neutralizing antibody at Visit 4/Day 43 will be calculated for the study interventions to demonstrate immunogenic superiority based on the protocol-defined superiority criterion.

4. Study Design

4.1. Overall Design

This Phase III study is designed as follows:

- Parallel group, prospective, randomized, double-blind, active-controlled, two-arm, multi-center.
- This study is aimed to recruit participants at approximately 2 study sites in the Republic of Paraguay in South American region.
- The participants, investigators, the site personnel and the Sponsor staff who are involved in the blinded conduct of the study will be blinded to the study intervention assignment until the termination of visit 5 when interim analysis is to be carried out. Preparation and administration of study intervention will be performed by authorized unblinded site personnel who do not participate in the evaluation of the participants.
- Approximately 1020 adult participants who are generally healthy or with stable pre-existing medical conditions and fulfill the entry criteria will be enrolled to achieve at least 942 participants randomly assigned to study intervention. An overall dropout rate of approximately 12% is assumed, from which participants may be excluded from the primary immunogenicity endpoint evaluation. The minimum number of participants required for the primary immunogenicity endpoint is 834 participants (see Section 9.5).

  Note: *Enrolled* means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process and screening.
- Randomization of participants will be stratified by study site(Section 6.3.1).
- Eligible participants will be randomized to one of the two parallel treatment groups to receive either MVC-COV1901 or AZD1222 in a 1:1 ratio:
  a. MVC-COV1901 (test product): approximately 471 participants will receive 2 doses of MVC-COV1901 (15 μg of S-2P protein/0.5 mL/dose)
  b. AZD1222 (active control): approximately 471 participants will receive 2 doses of AZD1222 (according to the approved dose of 0.5 ml)
- Treatment dosage and route of administration: each participant will receive 2 doses of MVC-COV1901 or AZD1222, administered 28 days apart via IM injection in the deltoid region, preferably of the nondominant arm, at Visit 2/Day 1 and Visit 3/Day 29.
- Study details include:
  a. The study duration per participant will be approximately 237 days (28 days screening, 29 days treatment, and 180 days follow-up).
  b. The treatment duration will be approximately 29 days.
  c. The study will consist of 7 on-site visits (1 screening visit, 2 treatment visits, and 4 follow-up visits):
     i. Day -28 to Day 1, Visit 1 (Screening)
     ii. Day 1, Visit 2 (First dose of study intervention)
     iii. Day 29 ± 3 days, Visit 3 (Second dose of study intervention)
     iv. Day 43 ± 3 days, Visit 4
     v. Day 57 ± 3 days, Visit 5

vi. Day 119 ± 14 days, Visit 6
vii. Day 209 ± 14 days, Visit 7

Visit 1 (screening) and Visit 2/Day 1 may be performed on the same day, in which case the assessments required for Visit 1 and Visit 2 will only need to be performed once (before the first dose of study intervention).

Unscheduled visit(s) may be arranged when deemed necessary by the investigator or study medical monitor.

- An IDMC will be established for this study to evaluate cumulative SAEs and other relevant safety data monthly and make appropriate recommendations to the Sponsor (see Section 10.1.5 for more details).
- One interim analysis is planned to be performed after all participants have completed Visit 5/Day 57 assessments. The primary and secondary immunogenicity and safety endpoints, as well as the exploratory endpoints of antigen specific antibody titers will be analyzed in the interim analysis if available before data cutoff date.

4.2. Study Management During the COVID-19 Pandemic

Due to the COVID-19 pandemic additional measures may need to be implemented for reasons which might include a study participant being in self-isolation/quarantine, limited access to public places (including hospitals) due to the risk of spreading infection, and the availability of study staff to perform visits. These challenges could have an impact on the study protocol including the completion of study assessments, study visits or the provision of study intervention. The safety of the study participants is of primary importance.

Actions undertaken due to the COVID-19 pandemic will be proportionate and based on benefit-risk considerations, with priority given to the impact on the health and safety of the study participant. The Sponsor will reassess risks as the situation develops and document any reassessment in the TMF. If an investigator-driven risk assessment might be necessary, this assessment will be documented in the investigator's site master file and communicated to the Sponsor.

Any changes to study conduct initiated by the Sponsor will be agreed with and communicated clearly to the investigators. If there is a need for an investigator to initiate a change to study conduct because of an urgent safety measure, the change will be reported as soon as possible by the investigator to the Sponsor. Study participants will be informed by the investigator, in a timely manner, about changes in the conduct of the clinical study relevant to them (e.g., cancellation of visits, a change in laboratory testing, or delivery of study intervention).

Changes in the distribution of the study intervention may be necessary to prevent avoidable visits to sites and to provide the study participants with needed treatments. If it becomes necessary, the Sponsor will assess the risks relating to the product and consider any alternative arrangements of study intervention administration in the participants.

The Sponsor will maintain appropriate records of all changes due to the COVID-19 pandemic that need to be implemented in the study master file. Any necessary mitigating measures will be

detailed in an appropriate protocol amendment in accordance with all applicable regulatory requirements.

4.3. Scientific Rationale for Study Design

This study is designed as a randomized, double-blind, active-controlled study to assess the immunogenicity, safety, and tolerability of MVC-COV1901 compared to the active control AZD1222. Participants will be randomized to the 2 treatment groups before the first dose of study intervention to minimize bias in the treatment assignment. Randomization in a 1:1 ratio will ensure balanced distribution of participants of various demography and baseline characteristics between the treatment groups.

The colors of the study interventions in suspension are slightly different, i.e., opalescent for MVC-COV1901 after shaking and colorless to slightly brown/opaque for AZD1222. Therefore, blinding is guaranteed by adopting an double-blind approach – preparation and administration of study intervention will be performed by authorized unblinded site personnel who do not participate in the evaluation of the participants (Section 6.2), whereas the participants, investigators, the site personnel and the Sponsor staff who are involved in the blinded conduct of the study will be blinded to the study intervention assignment until termination of visit 5..

As a number of COVID-19 vaccines have been approved and mass vaccination campaigns implemented in various countries, a placebo-controlled clinical study does not serve the public clinical interest and may not be considered ethical. Under the same circumstance and on the same ethical reason, recommendations have been made to switch investigational strategies from Phase III efficacy studies for COVID-19 vaccine, often involving large number of participants and long follow-up duration, to comparative studies (Dal-Ré et al. 2021; Fleming et al. 2021; Knottnerus 2021). Recent availability of early reports on the correlate of protection for COVID-19 vaccines (Earle et al. 2021; Jin et al. 2021; Khoury et al. 2021) further encourages the clinical study design of comparing candidate vaccine with an active comparator which has established efficacy and has been evaluated over an extended duration. The current study adopts a comparative immunogenicity design to primarily compare the anti-SARS-CoV-2 neutralizing antibody titers after 2 doses of MVC-COV1901 with that of the approved AZD1222, with the aim to establish immunogenic superiority.

The primary immunogenicity endpoint to test for immunogenic superiority in this study is determined based on the available clinical data of MVC-COV1901 and AZD1222 vaccines. The overall immunogenicity profiles of MVC-COV1901 and AZD1222 were similar in that both vaccines were able to elicit neutralizing antibodies and antigen specific immunoglobulin after the first dose of study intervention and slightly higher antibody levels at 14 days than at 28 days after the second dose of study intervention (Folegatti et al. 2020; Hsieh et al. 2021; unpublished data). The mean live virus and pseudovirus neutralizing antibody levels of AZD1222 at 14 days after the second dose of study intervention were similar to but generally tended to be lower than those of convalescent plasma samples (Folegatti et al. 2020; Khoury et al. 2021). Compared to AZD1222, the available data of MVC-COV1901 showed that the GMT of live virus (wild type) and pseudovirus neutralizing antibody in the 5, 15, and 25 μg treatment groups at 14 days after the second dose of study intervention were 0.8 to 3.9 times and 1.25 to 4.4 times the GMT of convalescent serum specimens, respectively (Hsieh et al. 2021). Therefore, the Sponsor

hypothesizes that MVC-COV1901 is immunogenic superior to AZD1222 in terms of neutralizing antibody titers at 14 days after the second dose of study intervention.

AZD1222 from AstraZeneca/Oxford University has shown a balanced benefit/risk profile based on the current available data. It is generally safe and well tolerated. It has a clinical efficacy of 59.5% based on the analysis of the efficacy endpoint on confirmed COVID-19 cases in participants aged 18 years and over who were seronegative at baseline, who had received two doses with a dose interval of 4 to 12 weeks, and who were on-study ≥ 15 days post second dose. Vaccine efficacy was 62.6% in participants receiving two recommended doses with any dose interval (ranging from 3 to 23 weeks) (Vaxzeria Summary of Product Characteristics). Apart from the balanced benefit/risk profile, AZD1222 is chosen as the active control in the study for the following reasons: a) the vaccine is commonly available in countries of the participating region, b) the vaccine has a similar range of storage temperature as the test product, i.e., 2 to 8^{o}C.

The study includes adult healthy participants and those with stable pre-existing medical conditions aged 18 years and above. The safety of the participants is ensured by implementing different measures of safety monitoring, including having an IDMC to review the safety data regularly throughout the study, all participants are also examined for any contraindication to the study intervention before and after each dose of study intervention. Throughout the study, MAAE, AESI, VAED, and SAE will be collected. AESIs include the immune-mediated AESIs as presented in the HEPLISAV-B® post hoc analysis (Hyer et al. 2018; Section 10.4) whereas VAEDs include AESIs relevant to COVID-19 vaccine identified by the Brighton Collaboration (SPEAC December 2020; Section 10.5). VAEDs have been described in nonclinical models for SARS and MERS in which candidate vaccines induced non-neutralizing antibodies and a T helper type 2-biased immune response, but a similar risk in humans is not known (Deming et al. 2006; Bolles et al. 2011; Honda-Okubo et al. 2015; Agrawal et al. 2016; Houser et al. 2017).

4.4. Justification for Dose

Nonclinical studies showed that S-2P protein at 5, 25, and 50 µg combined with CpG 1018 and $Al(OH)_3$ did not cause any significant adverse effects in the tested animals. Adjuvanted S-2P protein at 1 and 5 µg could induce high levels of neutralization antibody titers in the tested animals. In the clinical setting, 5, 15, and 25 µg S-2P protein with CpG 1018 and $Al(OH)_3$ adjuvants were investigated in the Phase I study (NCT04487210), and 15 µg S-2P protein was chosen for the Phase II study to compare with placebo (NCT04695652). All dose levels in both studies were safe and well tolerated, as well as able to induce the production of anti-SARS-CoV-2 neutralizing antibody and antigen specific immunoglobulin (see Section 2.2).

Based on the toxicology and immunogenicity profile of the vaccine in the nonclinical and clinical studies, 15 µg of S-2P protein is selected as the dose to be tested in this Phase III study.

4.5. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the schedule of activities (SoA) for the last participant in the study.

A participant is considered to have completed the study if he/she has completed the last scheduled procedure shown in the SoA.

5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Male or female participant aged 18 years and above at randomization.
2. Healthy adults or adults with pre-existing medical conditions who are in stable condition (obesity, endocrinological pathologies: diabetes, hyperthyroidism, hypothyroidism, etc., pneumopathies: asthma, emphysema, pulmonary fibrosis, cystic fibrosis, chronic obstructive pulmonary disease (COPD), heart diseases: arterial hypertension (HTN), arrhythmias, heart failure (HF), etc., liver diseases, renal, neurologic: angiographic cerebral vasospasm (ACV), psychiatric). A stable medical condition is defined as disease not requiring significant change in therapy or hospitalization for worsening disease 3 months before enrollment and expected to remain stable for the duration of the study.
3. Female participants:
    a. A female participant is eligible is the participant is a woman of non-childbearing potential, i.e., surgically sterilized (defined as having undergone hysterectomy and/or bilateral oophorectomy and/or bilateral salpingectomy; tubal ligation alone is not considered sufficient) or one year post-menopausal.
    b. If the participant is a woman of childbearing potential, she must agree to practice sexual abstinence or agree to use medically effective contraception from 14 days before screening to 30 days following the last administration of study intervention. Highly effective methods of contraception include:
        i. Implanted hormonal methods of contraception or placement of an intrauterine device or intrauterine hormonal-releasing system
        ii. Established use of hormonal methods (injectable, pill, patch, or ring) combined with barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository
        iii. Azoospermic partner (vasectomized or due to medical cause), provided the partner is the sole sexual partner of the female participant and the absence of sperm has been confirmed (from medical records/examination/history).
    c. Have a negative pregnancy test
4. Participant is willing and able to comply with all required study visits and follow-up required by this protocol.
5. Participant or the participant's legal representative must understand the procedures of the study and provide written informed consent.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

2. Pregnant or breast feeding or have plan to become pregnant within 30 days after the last administration of study intervention.
3. Employees at the investigator's site, of the Sponsor or delegate (e.g., contract research organization) who are directly involved in the conduct of the study.

Prior/Concomitant Therapy

4. Currently receiving or received any investigational intervention within 30 days prior to the first dose of study intervention.
5. Administered any licensed live-attenuated vaccines within 28 days or other licensed non-live-attenuated vaccines within 7 days prior to the first dose of study intervention.
6. Administered any blood product or intravenous immunoglobulin administration within 12 weeks prior to the first dose of study intervention.
7. Currently receiving or anticipate to receive concomitant immunosuppressive or immune-modifying therapy (excluding inhaled, topical skin and/or eye drop-containing corticosteroids, low-dose methotrexate, or < 2 weeks of daily receipt of prednisone less than 20 mg or equivalent) within 12 weeks prior to the first dose of study intervention.
8. Currently receiving or anticipate to receive treatment with tumor necrosis factor (TNF)-α inhibitors, e.g., infliximab, adalimumab, etanercept within 12 weeks prior to the first dose of study intervention.
9. Major surgery or any radiation therapy within 12 weeks prior to the first dose of study intervention.
10. Has received any other investigational or approved COVID-19 vaccine.

Medical Conditions

11. Immunosuppressive illness or immunodeficient state, including hematologic malignancy, history of solid organ, bone marrow transplantation, or asplenia.
12. A history of malignancy with potential risk for recurrence after curative treatment, or current diagnosis of or treatment for cancer (exceptions are squamous and basal cell carcinomas of the skin and treated uterine cervical carcinoma in situ, at the discretion of the investigator).
13. Bleeding disorder considered a contraindication to IM injection or phlebotomy.
14. Known SARS-CoV-2 infection in the 3 months prior to the first dose of study intervention.
15. A history of cerebral venous sinus thrombosis, heparin-induced thrombocytopenia or antiphospholipid syndrome.
16. Participant who, in the investigator's judgement, is not in a stable condition and by participating in the study could adversely affect the safety of the participant, interfere with adherence to study requirements or evaluation of any study endpoint. This may include a participant with ongoing acute diseases, severe infections, autoimmune disease, laboratory abnormality or serious medical conditions in the following systems: cardiovascular, pulmonary, hepatic, neurologic, metabolic, renal, or psychiatric.
17. A history of hypersensitivity to any vaccine or a history of allergic disease or reactions likely to be exacerbated by any component of the MVC-COV1901 or AZD1222.
18. Body (oral, rectal, or ear) temperature ≥ 38.0°C or acute illness (not including minor illnesses such as diarrhea or mild upper respiratory tract infection at the discretion of the investigator) within 2 days before the first dose of study intervention.

5.3. Lifestyle Considerations

Participants are required to follow the contraceptive steps as outlined in Section 5.1. Restrictions relating to concomitant medications are described in Section 6.8.

5.4. Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently randomized to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and eligibility criteria.

Participants who have met the exclusion criteria under Prior/Concomitant Therapy (Section 5.2) may be rescreened once and reassessed for these criteria. A participant who is rescreened is not required to sign a new informed consent form (ICF) if the rescreening occurs within 28 days from the previous ICF signature date, otherwise they are required to undergo the informed consent process, assigned a new participant number, and to repeat the screening process.

5.5. Criteria for Temporarily Delaying Randomization/Administration of Study Intervention

The following conditions may allow a participant to be randomized/to start receiving study intervention once the conditions have resolved and the participant is otherwise eligible:

- Body (oral, rectal or ear) temperature ≥ 38.0°C or acute illness (not including minor illnesses such as diarrhea or mild upper respiratory tract infection at the discretion of the investigator) within 2 days before the *first* dose of study intervention
- Administration of any non-live-attenuated vaccine within 7 days before the *first* dose of study intervention
- Administration of any live-attenuated vaccine within 28 days before the *first* dose of study intervention

If any of these events occur before the scheduled time of the first dose of study intervention, randomization at a later date within the screening window is permitted at the discretion of the investigator and after consultation with the Sponsor. If randomization cannot occur within the screening window, rescreening is required.

6. Study Intervention(s) and Concomitant Therapy

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

Table 6.1 Study Intervention(s) Administered

Intervention Name	MVC-COV1901	AZD1222
Type	Vaccine	Vaccine
Dose Formulation	Recombinant S-2P protein formulated with CpG 1018 and $Al(OH)_3$ in phosphate buffered saline	Chimpanzee adenovirus encoding the SARS-CoV-2 spike glycoprotein (ChAdOx1-S), other excipients include L-histidine, L-histidine hydrochloride monohydrate, magnesium chloride hexahydrate, polysorbate 80 (E433), sucrose, disodium edetate (dihydrate), and water for injections
Unit Dose Strength(s)	15 µg of S-2P protein/0.5 mL/dose	Not less than 2.5×10^8 infectious units/0.5 mL/dose
Dosage Level(s)	2 doses at 28 days apart	2 doses at 28 days apart
Route of Administration	IM injection	IM injection
Use	Experimental	Experimental
IMP or NIMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor MEDIGEN VACCINE BIOLOGICS CORP.	Provided locally by Ministry of Public Health and Social Welfare, through the National Immunization Center (PAI) of the Republic of Paraguay

Packaging and Labeling	Study intervention will be provided in multidose vials. Each vial will be labeled as required per country requirement and requirements of the country's health surveillance service.	Study intervention will be provided in multidose vials. . Each vial is labeled according to the supplier as required per country requirements.

Abbreviation: IM = intramuscular; IMP = investigational medicinal product; NIMP = non-investigational medicinal product

Table 6.2 Study Treatment Groups

Treatment Title	MVC-COV1901	AZD1222
Treatment Type	Experimental	Active comparator
Treatment Description	Participants will receive 2 doses of vaccine containing 15 µg of S-2P protein, administered 28 days apart via IM injection at Visit 2/Day 1 and Visit 3/Day 29	Participants will receive 2 doses of vaccine at the approved dose strength, administered 28 days apart via IM injection at Visit 2/Day 1 and Visit 3/Day 29

Study intervention should be administered intramuscularly into the deltoid muscle, preferably of the nondominant arm. Administration of study intervention should be performed by appropriately qualified and trained personnel as allowed by local and institutional guidance.

Before IM injection of the study intervention, the local skin will be sterilized. After IM injection, participants will be observed for at least 30 minutes for any immediate adverse reactions, including local events (pain/tenderness, erythema/redness, and induration/swelling) and systemic events (fever, malaise/fatigue, myalgia, headache, nausea/vomiting, and diarrhea). Vital signs including blood pressure, respiratory rate, pulse/heart rate, and body temperature will be checked before the administration of study intervention and approximately 30 minutes after the administration of study intervention.

6.2. Preparation, Handling, Storage, and Accountability

6.2.1. Preparation and Handling

The study intervention (MVC-COV1901) used in this study will be prepared, packaged, and labeled under the responsibility of a qualified person from the Sponsor with Standard Operating Procedures (SOPs) of the Sponsor, Pharmaceutical Inspection Co-operation Scheme (PIC/S) Good Manufacturing Practice (GMP) guidelines, The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines, and applicable local law/regulations. The product will be labeled with

descriptions “Clinical trial use only” as well as other required information according to the local regulatory requirements in the local language.

The investigator will assign unblinded personnel who will be responsible to prepare the study intervention on the day of study intervention administration and to administer the study intervention to the participants.

6.2.2. Product Storage and Stability

The study intervention should be stored at 2-8°C and protected from light. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to authorized personnel.

The assigned unblinded personnel must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before the use of the study intervention.

6.2.3. Acquisition and Accountability

The Sponsor is responsible for supplying MVC-COV1901 to the study sites. The assigned unblinded personnel will conduct an inventory of the supplies, including dates, quantities, batch/serial numbers of each delivery, and verify that study intervention supplies are received intact and in the correct amounts before completing a supplies receipt.

Only participants randomized in the study may be administered with the study intervention and only the assigned unblinded personnel may supply or administer the study intervention to the participants. The assigned unblinded personnel must correctly document the amount of the study intervention administered on the provided dispensing log.

The assigned unblinded personnel will be responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records). Any discrepancy noted will be investigated, resolved, and documented prior to returning or destruction of unused study intervention. All study intervention must be retained until the study monitor has confirmed the accountability and the Sponsor has given instruction for the final disposition of unused study intervention. Further guidance will be provided, unused study intervention should either be returned to the Sponsor for destruction or destroyed at the study site according to standard institutional procedures after drug accountability has been conducted by the Sponsor or delegate.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Randomization

Eligible participants will be randomized to receive either MVC-COV1901 or AZD1222 in a 1:1 ratio. Simple random sampling will be used to select study participants by study site. Approximately 471 participants will be randomized to each of the study intervention group.

Study intervention will be administered at the study visits as summarized in the SoA (Section 1.3).

6.3.2. Blinding

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Sponsor prior to unblinding a participant's intervention assignment unless this could delay emergency treatment for the participant. If a participant's intervention assignment is unblinded, the Sponsor must be notified within 24 hours of this occurrence. The date and reason for the unblinding must be recorded.

The IDMC will review the safety data in a blinded manner. The IDMC and/or Sponsor may unblind the intervention assignment for any participant with an AE/SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or Sponsor policy.

This is a double-blind study in which participants, investigators, the site personnel, and the Sponsor staff who are involved in the blinded conduct of the study are blinded to study intervention until the termination of visit 5 so that planned interim analysis can be conducted for early detection of reliable evidence of primary and secondary immunogenicity and safety endpoints. To maintain this blind, the investigator will assign authorized unblinded personnel who will not be involved in any other aspect of the study conduct to handle the preparation, dispensing, administration, and accountability of the study intervention. Study-specific training will be provided to the study site to ensure treatment blind of the investigators, all other site personnel, and the participants.

In the event of a quality assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been conducted accurately.

6.3.3. Unblinding

Once Visit 5/Day 57 is completed, a planned interim analysis is to be carried out to evaluate primary and secondary immunogenicity and safety endpoints, as well as the exploratory immunogenicity endpoint of antigen specific antibody titers. The results of the interim analysis will be submitted to DINAVISA for evaluation and regulatory decision making to comply with local requirements.

During this time, the ongoing study integrity will be maintained. Participants, investigators, site personnel, local regulators, and the sponsor staff will be unblinded to the individual treatment group assignments.

Participants will be provided with a new immunization card with the record of which vaccine the participant has received according to the local regulations of the health authorities.

6.4. Study Intervention Compliance

Participants will receive 2 doses of study intervention at the site directly from the assigned unblinded personnel of the study, under medical supervision at the site. The study monitor will assure the participant's compliance with the study protocol. The date and time of each dose administered at the site and the number of study intervention administered will be recorded in the source documents. The dose of study intervention and study participant identification will be confirmed at the time of dosing by the unblinded personnel administering the study intervention.

6.5. Dose Modification

No dose modification is allowed in the study.

If, in the opinion of the investigator, a participant is unable to tolerate the assigned study intervention and should discontinue the study intervention, he/she may remain in the study, if deemed appropriate by the investigator, to complete all scheduled visits and assessments as described in the SoA (Section 1.3), or they may be withdrawn from the study and follow the procedures outlined in Section 7.2.

6.6. Continued Access to Study Intervention after the End of the Study

No study intervention will be provided to study participants at the end of the study.

6.7. Treatment of Overdose

Study intervention overdose is rare given the participants will receive study intervention directly from the authorized unblinded personnel assigned by the investigator.

In rare instances of suspected overdose, the investigator should determine if there is any immediate medical treatment needed. The participant should be evaluated before continuing any further study activities and closely monitored for any AE or SAE and laboratory abnormalities. The investigator should report the event to the Sponsor or delegate as soon as possible. Any unfavorable effects caused by the overdose event must be reported as an AE or SAE.

6.8. Prior and Concomitant Therapy

Concomitant therapy is defined as any therapy including surgeries, vaccines, or prescribed medication taken after the start of administration of study intervention. Participants are allowed to receive routinely used medications or treatments for other indications which is judged by the investigator as not affecting the immunogenicity and safety assessments of this study.

Any medication (including over-the-counter or prescription medicines) or vaccine that the participant is receiving prior and at the time of enrollment and during the study must be recorded on the appropriate page of the case report form (CRF).

Therapies will be categorized as follows:

- Vaccines of any kind will be recorded from 28 days prior to the first dose of study intervention until end of study (EOS)
- Immunoglobulins and/or other blood products will be recorded from 12 weeks prior to the first dose of study intervention until EOS
- Systemic steroids or other immune-modifying agents will be recorded from 12 weeks prior to the first dose of study intervention until EOS
- Treatment with TNF-α inhibitors will be recorded from 12 weeks prior to the first dose of study intervention until EOS
- Major surgeries and radiation therapy will be recorded within 5 years prior to the first dose of study intervention until EOS
- All other medications will be recorded up to 6 weeks prior to the first dose of study intervention until EOS

The name of the therapy, frequency, unit dose, routes, dates of when the drug/therapy started and stopped (if medication/therapy is not ongoing), and the indication for the use of the drug/therapy will be recorded.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.8.1. Prohibited Therapy/Medication

The following therapies/medications are prohibited in the study or under the specified condition:

- Major surgery or any radiation therapy within 12 weeks prior to the first dose of study intervention and during the study
- Immunoglobulins and/or other blood products within 12 weeks prior to the first dose of study intervention and during the study
- Immunosuppressant (excluding inhaled, topical skin and/or eye drop-containing corticosteroids, low-dose methotrexate, or < 2 weeks of daily receipt of prednisone of < 20 mg or equivalent) within 12 weeks prior to the first dose of study intervention and during the study
- TNF-α inhibitors, e.g., infliximab, adalimumab, or etanercept, within 12 weeks prior to the first dose of study intervention and during the study
- Any other investigational intervention within 30 days prior to the first dose of study intervention and during the study
- Administration of any licensed live-attenuated vaccine within 28 days prior to or after each dose of study intervention
- Administration of any licensed non-live-attenuated vaccine within 7 days prior to or after each dose of study intervention
- Any other investigational or approved COVID-19 vaccine during the study

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

Upon the start of study intervention on Day 1, participants will be assessed throughout the study if they meet any of the elimination criteria. It may be necessary for a participant to discontinue the second dose of study intervention if any of the following discontinuation criteria is met:

- Administration of prohibited therapy/medication
  Note: Participants could receive the second dose of study intervention after 7 days of non-live-attenuated vaccine or after 28 days of live-attenuated vaccine administration (see Section 7.1.1).
- Confirmed COVID-19 based on available medical records
- Any pathological event, clinical AE, or any change in the participant's condition giving indication to the investigator that further participation in the study may not be in the best interest of the participant
- Pregnancy (Section 8.3.10)
- Any vaccine-related SAE during the study period

If study intervention is permanently discontinued, the participant will remain in the study if deemed appropriate by the investigator to complete all scheduled visits and assessments as described in the SoA (Section 1.3).

7.1.1. Contraindication to Study Intervention

Prior to each administration of study intervention at Visit 2/Day 1 and Visit 3/Day 29, participants will be assessed for contraindication criteria to the study intervention. Participants who meet any of the following criteria will either be rescheduled for administration of study intervention within the visit window, or they may be requested to discontinue study intervention or be withdrawn from the study if deemed necessary by the investigator:

- Body (oral, rectal or ear) temperature ≥ 38.0°C or acute illness (not including minor illnesses such as diarrhea or mild upper respiratory tract infection at the discretion of the investigator) within 2 days before each dose of study intervention
- Any non-live-attenuated vaccine within 7 days before each dose of study intervention
- Any live-attenuated vaccine within 28 days before each dose of study intervention
- Any condition that is a contraindication to study intervention based on the judgement of the investigator

See Section 5.5 if participants meet the above criteria prior to the first dose of study intervention. In circumstances that participants cannot be rescheduled for administration of the second dose of study intervention within the visit window, they will still be encouraged to complete the 2 doses of study intervention, and the out-of-visit-window administration of study intervention will be recorded on the CRF.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request. A participant may also be withdrawn at any time at the discretion of the investigator for the following safety, behavioral, or compliance reasons:

- If they meet any of the discontinuation criteria (Section 7.1) or contraindication to study intervention (Section 7.1.1)
- Lost to follow-up (Section 7.3)
- Non-compliant with the study procedure or study schedule
- The study is terminated prematurely by the investigator, research institution, Sponsor, institutional review boards (IRBs)/independent ethics committees (IECs) or regulatory authorities (Section 10.1.9)

At the time of discontinuing from the study, if possible, an early termination (ET) visit should be conducted, as shown in the SoA (Section 1.3). See SoA for data to be collected at the time of study withdrawal.

The reason for ET must be recorded on the CRF. If a participant withdraws from the study due to an AE, every effort will be made to follow the event until it resolves or stabilizes at a level acceptable to the investigator. For a participant who withdraws voluntarily, the study staff may contact them to obtain further safety information and to inform them of any significant findings which may affect their safety or health, unless the participant specifies unwillingness to be contacted again.

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

7.3. Lost to Follow up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant. These contact attempts should be documented in the participant’s medical record or study file.

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Unscheduled visit(s) may be arranged for a participant during the study, which may be prompted by reactogenicity issues, new or ongoing AEs or abnormal clinical presentation.

The type of biological samples to be collected during the study is provided in Section 8.5.

8.1. Immunogenicity Assessments

Blood samples for immunogenicity evaluation will be collected from all participants according to the SoA (Section 1.3). At Visit 2/Day 1 and Visit 3/Day 29, blood samples will be collected before the administration of study intervention. Additionally, blood samples will be collected from participants who are withdrawn from the study at the ET visit if the ET visit is performed at least 14 days after the previous blood sampling for immunogenicity.

The actual time and date of each sample collected will be recorded in the CRF, and unique identification number of the participants will be used to maintain the blind at the laboratory at all times and to allow for automated sample tracking and storage. Handling and preparation of the samples for analysis, as well as shipping and storage requirements, will be provided in a separate study manual.

Samples will be stored for the duration required by local regulations and under the condition according to local regulations at the central laboratories or at a facility selected by the Sponsor following the last participant’s last visit in the study.

8.1.1. Anti-SARS-CoV-2 Neutralizing Antibody

Anti-SARS-CoV-2 neutralizing antibody titers will be evaluated in the blood (serum) samples collected. The detection and characterization of anti-SARS-CoV-2 neutralizing antibody will be performed by central laboratories in Taiwan using validated live virus and/or pseudovirus neutralization assays.

8.1.2. Antigen specific antibody

Antigen specific antibody titers will be evaluated in the blood (serum) samples collected. The detection and characterization of antigen specific antibody will be performed by the delegated central laboratory using validated enzyme-linked immunosorbent assay (ELISA).

8.2. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Section 1.3).

8.2.1. Demographics and Medical History

Demographic information of the participants, including sex, age, race, place of residence, height, weight, and body mass index (BMI), and other baseline characteristics will be collected at screening and recorded on the appropriate CRF page.

Medical history of the participants will be collected at screening and recorded on the Medical History CRF page. Any significant medical conditions that are present prior to the first dose of study intervention will also be included in the Medical History CRF page.

The following medical history should be recorded:

- General medical history within 12 weeks prior to the first dose of study intervention
- Serious medical conditions, including cardiovascular, hepatic, psychiatric condition, medical history, physical findings, or laboratory abnormality within 2 years prior to the first dose of study intervention
- History of malignancy, major surgery, and inflammatory or degenerative neurological disease within 5 years prior to enrollment

All history recorded will include the date of onset, diagnosis and current status.

8.2.2. Physical Examinations

A complete physical examination will be conducted at screening and will include general appearance, skin, eyes, ears, nose, throat, head and neck, heart, chest and lungs, abdomen, extremities, lymph nodes, musculoskeletal, and neurological. A targeted physical examination will be conducted at all subsequent visits as indicated in the SoA (Section 1.3), and at any unscheduled visit as required by the investigator during which the investigator will examine if there is any indication of change in the participant's health since the previous visit. Physical examination scheduled for Visit 2/Day 1 and Visit 3/Day 29 will be performed before the administration of study intervention.

Investigators should pay special attention to clinical signs related to previous serious illnesses. The investigator will review all physical examination findings for clinical significance. Any findings from the physical examination during the study will be recorded on the CRF.

Any clinically significant change in the physical examination findings after the first dose of study intervention should be recorded as an AE.

8.2.3. Vital Signs

Vital signs will be measured at screening, Visit 2/Day 1, and Visit 3/Day 29 before the administration of study intervention, approximately 30 minutes after the administration of study intervention, and at any unscheduled visit as required by the investigator. Vital signs will include body temperature, systolic and diastolic blood pressure, pulse rate, and respiratory rate.

All vital sign readings will be documented in the CRF. The investigator will review all vital sign values for clinical significance. Additional vital signs will be obtained when clinically indicated.

Any clinically significant change in the vital signs after the first dose of study intervention should be recorded as an AE.

8.2.4. Clinical Safety Laboratory Tests

Clinical safety laboratory tests will be performed at screening and at any unscheduled visit as required by the investigator. Clinical safety laboratory tests will include hematology, biochemistry, immunology, and serology. Hematology, biochemistry, and immunology tests at screening will provide a point of reference for the evaluation of AEs during the study, if needed. The protocol-required laboratory tests are as defined in Section 10.2.

Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the participant's condition.

All clinical safety laboratory assessments will be carried out by the company Meyer lab, and Fundación del Hospital Tesai or delegated lab, if necessary, that has the qualifications and certificates required by local authorities, and in accordance with the SOP or laboratory manual. All results of the safety laboratory measurements will be reported to the investigator and must be recorded in the CRF.

Any clinically significant changes in the clinical safety laboratory assessments occurring at an unscheduled visit during the study should be recorded as an AE.

8.2.5. Pregnancy Testing

A pregnancy test (beta human chorionic gonadotropin [hCG]) for participants of childbearing potential will be performed at screening, before each dose of study intervention at Visit 2/Day 1 and Visit 3/Day 29, Visit 4/Day 43, and Visit 5/Day 57.

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator, or required by local regulation, to establish the absence of pregnancy at any time until 30 days after the last administration of study intervention.

8.2.6. Participant Diary

Participants will be required to complete a participant diary after the administration of study intervention and must be instructed to record any solicited local and systemic AEs, unsolicited AEs, and concomitant medication used.

The following local AEs will be solicited: pain/tenderness, erythema/redness, induration/swelling, bruising and pruritus; and the following systemic AEs will be solicited: fever, malaise/fatigue, myalgia, headache, nausea/vomiting, diarrhea, chillness and joint pain. At each dosing, participants will be instructed on how to self-assess solicited AEs such as measuring body temperature, injection site erythema and swelling; participants will also record the timing and intensity of the AEs according to the toxicity grading scales defined in Section 8.3.6.1, and whether medication was taken to relieve the events.

In the participant diary, erythema/redness and induration/swelling at the injection site will be recorded as the greatest surface diameter in millimeter (mm), and the maximum oral temperature will be recorded in °C.

Solicited AEs will be collected on the day of administration of study intervention and on the 7 subsequent days, whereas unsolicited AEs will be collected on the day of administration of study intervention and on the 28 subsequent days. Any solicited AE that is ongoing beyond Day 8 will be recorded in the participant diary until resolution. AEs recorded in the participant diary after each dose of study intervention should be reviewed by study staff at the next study site visit.

The investigator or designee must obtain further information from the participant for any ongoing solicited local and systemic events, unsolicited AEs, and use of concomitant medication beyond the usage of the participant diary. The collected information should be documented in the source documents and the information entered in the CRF.

8.3. Adverse Events (AEs) Serious Adverse Events (SAEs), and Other Safety Reporting

The definitions of AEs and SAEs can be found in Section 10.3.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE (Section 10.3.1) or SAE (Section 10.3.2) and remain responsible for following up all AEs including SAEs, MAAEs (Section 8.3.7), AESI (Section 8.3.8), VAED (Section 8.3.9), AEs considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention and/or study (see Section 7).

The method of recording and follow-up of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.3 and Section 10.3.4.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs (including MAAEs, AESI, and VAED) and SAEs will be collected from the start of study intervention until the end of the study at the timepoints specified in the SoA (Section 1.3).

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as medical history, not as AEs.

All SAEs will be recorded and reported to the Sponsor or delegate immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3.3. The investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

8.3.2. Method of Detecting AEs and SAEs

At every study visit, participants will be asked for any medically related changes in their well-being. They will also be asked if they have been hospitalized, have had any accidents, used any new medications, or changed concomitant medication regimens. Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

AEs will also be collected through voluntary reporting by the participant or, when appropriate, by the participant's legally authorized representative.

8.3.3. Follow-up of AEs and SAEs

After the initial AE or SAE report, the investigator is required to proactively follow each participant at subsequent visits. All AEs including SAEs, MAAEs, AESI, and VAED will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.3).

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the Sponsor or delegate of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor or delegate has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

The Sponsor or delegate will notify the regulatory authorities of any unexpected fatal or life-threatening adverse reaction as soon as possible, but no later than 7 calendar days after Sponsor's first knowledge of the event. A complete report should be provided within 15 calendar days after Sponsor's first knowledge of the event and must include an assessment of the importance and implication of the findings and/or previous experience on the same or similar medical products (ICH E2A 1994).

Any suspected unexpected serious adverse reaction (SUSAR) that is not fatal or life-threatening must be filed as soon as possible but no later than 15 calendar days after Sponsor's first knowledge of the event (ICH E2A 1994). Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

8.3.5. Assessment of Intensity and Causality of AEs and SAEs

8.3.5.1. Intensity of AE and SAE

The intensity of an AE or SAE will be assessed by the investigator based on the extent to which it affects the participant's daily activities (Table 8.1). Changes in the intensity of an AE or SAE should be documented in the participant's source documents to assess the duration of the event at each level of intensity.

An event is defined as "serious" when it meets at least one of the predefined outcomes as described in the definition of an SAE (Section 10.3.2), not when it is rated as severe.

Table 8.1 Intensity Grading of Adverse Events

Systemic Illness	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially life threatening (Grade 4)
Illness or clinical AEs	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	Hospitalization[#]

Source: modified from the US FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007 (FDA CBER Guidance 2007).
Note:
Modified by the Sponsor
Medical intervention is defined as use of any therapy intended to change the natural outcome of an event, eg, use of antibiotics to treat infection, other etiological treatment instead of symptomatic relief.
The definition of activity in Grade 2 refers to instrumental activities of daily living (ADL), such as preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
The definition of daily activity in Grade 3 refers to self-care ADL, such as bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
Only an event beyond Grade 3 which results in hospitalization will be assessed as Grade 4.

In case of death, the intensity grading will be assessed as Grade 5.

8.3.5.2. Causality of AE and SAE

The causality assessment is one of the criteria used when determining regulatory reporting requirements. The investigator is obligated to assess the relationship between study intervention and each occurrence of AE or SAE based on their clinical judgment. The investigator will also consult the Investigator's Brochure or product information for marketed products in his/her assessment. For each AE or SAE, the investigator must document in the medical notes that he/she has reviewed the AE or SAE and has provided an assessment of causality.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.

There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the Sponsor or delegate. However, it is very important that the investigator always assess the causality for every event before the initial transmission of the SAE data to the Sponsor or delegate. The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

The causality of AEs and SAEs will be assessed according to the categories in Table 8.2 below:

Table 8.2 Causality Assessment of Adverse Events

Causality	Description
Definitely related	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study agent/intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study agent/intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
Probably related	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time sequence to administration of the study agent/intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
Possibly related	There is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an adverse drug event may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
Unlikely to be related	A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the investigational product) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
Not related	The AE is completely independent of study agent/intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the investigator.

8.3.6. Solicited and Unsolicited Adverse Events

Solicited AEs

Solicited AEs are defined as AEs listed below which occurred within 7 days after each dose of study intervention:

- *Local events*: pain/tenderness, erythema/redness, induration/swelling, bruising and pruritus
- *Systemic events*: fever, malaise/fatigue, myalgia, headache, nausea/vomiting, diarrhea, chillness, and joint pain

For detection of solicited AEs, participants will be instructed to record the AEs in a participant diary for the predefined duration (Section 8.2.6).

Solicited AEs should not be reported as unsolicited AEs. If a solicited AE fulfills the definition of an SAE (Section 10.3.2) or MAAE (Section 8.3.7), the AE must be recorded on the respective page of the CRF, and the SAE reported according to the process described in Sections 8.3.4 and 10.3.4.

Unsolicited AEs

Unsolicited AEs are defined as any untoward medical events other than solicited AEs which occurred within 28 days after each dose of study intervention.

For detection of unsolicited AEs, participants will be instructed to record the AEs in a participant diary for the predefined duration (Section 8.2.6).

If an unsolicited AE fulfills the definition of an SAE (Section 10.3.2), MAAEs (Section 8.3.7), AESI (Section 8.3.8), or VAED (Section 8.3.9), the AE must be recorded on the respective page of the CRF. The SAE must be reported according to the process described in Sections 8.3.4 and 10.3.4. See Section 8.3.8 and Section 8.3.9 for reporting AESI and VAED, respectively.

Further definitions of solicited and unsolicited AEs can be found in Section 10.3.1.

8.3.6.1. Intensity of Solicited and Unsolicited Adverse Events

The intensity of solicited and unsolicited AEs will be graded according to the grading scales which are modified from the US FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007 (FDA CBER Guidance 2007).

The intensity grading for solicited local and systemic AEs are provided in Table 8.3 and Table 8.4, respectively, below.

Table 8.3 Solicited Local Adverse Events and Intensity Grading

Local events	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially life threatening (Grade 4)
Pain/Tenderness#	Does not interfere with activity; mild discomfort to touch	Repeated use of non-narcotic pain reliever for > 24 hours or interferes with activity; discomfort with movement	Any use of narcotic pain reliever or prevents daily activity; significant discomfort at rest	Hospitalization#
Erythema/Redness*	25 – 50 mm	51 – 100 mm	> 100 mm	Necrosis or exfoliative dermatitis
Induration/Swelling**	25 – 50 mm and does not interfere with activity	51 – 100 mm or interferes with activity	> 100 mm or prevents daily activity	Necrosis
Bruising	<10 mm#	10 – 25 mm#	> 25 mm#	Hospitalization#
Pruritus	No interference with activity	Some interference with activity	Significant; prevents daily activity	Hospitalization#

Note:
Modified by the Sponsor.
* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.
** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.
"Grade 0 (None)" will be recorded for Erythema/Redness, or Induration/Swelling < 25 mm.
The definition of activity in Grade 2 refers to instrumental ADL, such as preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
The definition of daily activity in Grade 3 refers to self-care ADL, such as bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
Only an event beyond Grade 3 which results in hospitalization will be assessed as Grade 4.

Table 8.4 Solicited Systemic Adverse Events and Intensity Grading

Systemic events	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially life threatening (Grade 4)
Fever (°C) *	38.0 – 38.4	38.5 – 38.9	39.0 – 40	> 40
Malaise/Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	Hospitalization#
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	Hospitalization#
Headache	No interference with activity	Repeated use of nonnarcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	Hospitalization#
Nausea/Vomiting	No interference with activity or 1 – 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient intravenous (IV) hydration	Hospitalization for hypotensive shock#
Diarrhea	2 – 3 loose stools or < 400 g/24 hours	4 – 5 stools or 400 – 800 g/24 hours	6 or more watery stools or > 800 g/24 hours or requires outpatient IV hydration	Hospitalization for hypotensive shock#
Chillness	No interference with activity	Some interference with activity	Significant; prevents daily activity	Hospitalization#
Joint pain	No interference with activity	Some interference with activity	Significant; prevents daily activity	Hospitalization#

Note:
Modified by the Sponsor.
* The temperature ranges indicated in the table are based on oral temperature.
The definition of activity in Grade 2 refers to instrumental ADL, such as preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
The definition of daily activity in Grade 3 refers to self-care ADL, such as bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
Only an event beyond Grade 3 which results in hospitalization will be assessed as Grade 4.

Intensity of unsolicited AEs will be assessed based on the classification of all AEs other than solicited AEs as described in Section 8.3.5.1.

8.3.6.2. Causality of Solicited and Unsolicited Adverse Events

All solicited local AEs will be considered causally related to the study intervention.

Causality of solicited systemic AEs and unsolicited AEs will be assessed based on the classification of all other AEs as described in Section 8.3.5.1.

8.3.7. Medically Attended Adverse Events

MAAEs are defined as AEs leading to medically attended visits that are not the scheduled study visits, such as an emergency room visit or an unscheduled visit to a healthcare practitioner/clinic outside of the study site. AEs, including abnormal physical examination findings and abnormal vital signs, identified on a scheduled study visit will not be considered MAAEs.

Investigators will review all AEs, including unsolicited AEs (see Sections 8.3.5, 10.3.1) for the occurrence of any MAAEs. All MAAEs must be recorded on the MAAE page of the CRF.

8.3.8. Adverse Events of Special Interest

An AESI (serious or non-serious) is one of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the Sponsor could be appropriate. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the Sponsor to other parties (e.g., regulators) might also be warranted (ICH E2F 2010).

AESIs will be collected according to the timepoints specified in the SoA (Section 1.3). AESIs defined for this study are provided in Section 10.4. All AESIs will be recorded on the AESI page of the CRF.

The investigator must report any occurrence of AESI to the Sponsor or delegate within 24 hours of the investigator's knowledge of the event, regardless of the expectedness and causality to the study intervention. Other supporting documentation of the event may be requested by the Sponsor or delegate and should be provided as soon as possible.

If the AESI is also an SAE, it should be reported according to the process described in Sections 8.3.4 and 10.3.4, and indicate it as an AESI in the SAE reporting form.

8.3.9. Vaccine-Associated Enhanced Diseases

VAEDs will be collected according to the timepoints specified in the SoA (Section 1.3). VAEDs defined for this study are provided in Section 10.5. All VAEDs will be recorded on the VAED page of the CRF.

The investigator will report to the Sponsor or delegate any occurrence of VAED within 24 hours of the investigator's knowledge of the event, regardless of the expectedness and causality to the study intervention. Other supporting documentation of the event may be requested by the Sponsor or delegate and should be provided as soon as possible. Additional result of pathogen isolation or molecular biological test for viral (SARS-CoV-2) RNA should be provided in the assessment of VAED (Section 10.5).

If the VAED is also an SAE, it should be reported according to the process described in Sections 8.3.4 and 10.3.4, and indicate it as a VAED in the SAE reporting form.

8.3.10. Pregnancy

If the participant becomes pregnant before the first dose, she will not receive any dose from the study determination and will be excluded from the study. If the participant becomes pregnant between the first and second doses, she will not receive the second dose of the study intervention and would continue in the study protocol to follow up on the immunogenicity and safety. If the participant becomes pregnant after receiving two doses of study intervention, the participant will continue in the study protocol to follow up the safety and determine immunogenicity, since no increased risk is established for blood extractions. Regarding the follow-up of pregnancy and its effects, it will depend on: if the pregnancy occurs within 30 days after vaccination, the follow-up will be carried out until the end of the pregnancy; if the pregnancy occurs after 30 days of receiving the second dose, there will be no need to follow up.

Details of pregnancies in female participants will be collected after the start of study intervention and until after 30 days following the last administration of study intervention. If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the Sponsor or delegate.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such per Sections 8.3.4 and 10.3.4. Reporting of pregnancy cases to the regulatory authorities and IRBs/IECs will follow the local regulations.

The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the Sponsor or delegate.

Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the Sponsor or delegate. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue study intervention but may remain in the study, if deemed appropriate by the investigator, to complete all scheduled visits and assessments as described in the SoA (Section 1.3).

8.4. Exploratory Efficacy Assessments

Efficacy of study intervention will be assessed in all treated participants in an exploratory manner through COVID-19 cases confirmed by laboratory reverse transcription polymerase chain reaction (RT-PCR) test starting from Day 1 in the study.

The definitions of laboratory-confirmed symptomatic COVID-19 and laboratory-confirmed severe COVID-19 are modified from US FDA recommendation (FDA COVID-19 Vaccine 2020):

- Laboratory-confirmed symptomatic COVID-19: laboratory reverse transcription polymerase chain reaction (RT-PCR) confirmed SARS-CoV-2 infection (sampling during, or within 4 days before or after, the symptomatic period) with one or more of the following symptoms:
    - Fever or chills
    - Cough
    - Shortness of breath or difficulty breathing
    - Fatigue
    - Muscle or body aches
    - Headache
    - New loss of taste or smell
    - Sore throat o Congestion or runny nose
    - Nausea or vomiting
    - Diarrhea
- Laboratory-confirmed severe COVID-19: laboratory-confirmed symptomatic COVID-19 with any of the following:
    - Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥ 30 per minute, heart rate ≥ 125 per minute, SpO2 ≤ 93% on room air at sea level or PaO2/FiO2 < 300 mm Hg)
    - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or ECMO)
    - Evidence of shock (SBP < 90 mm Hg, DBP < 60 mm Hg, or requiring vasopressors)
    - Significant acute renal, hepatic, or neurologic dysfunction
    - Admission to an intensive care unit (ICU)
    - Death attributed to a complication of COVID-19

  Note: The onset date of the COVID-19 case will be the date that symptoms were first experienced by the participant. With regard to the asymptomatic SARS-CoV-2 infection, the onset date of SARS-CoV-2 infection will be the earliest collection date of the sample that confirmed SARS-CoV-2 positive by RT-PCR.

Information of suspected COVID-19 will be collected at each visit. Participants will be asked if they experience any symptom or illness which may indicate SARS-CoV-2 infection or COVID-19. If a participant meets the reporting requirements for COVID-19 defined by the local regulatory authority, the study staff will instruct the participant to take appropriate follow-up action as required per local regulation. The applicable local guideline should be followed for the clinical management of suspected and confirmed cases, such as molecular diagnostic, isolation of infected participants in a health facility, and provision of treatments for infected participants.

Participants who have laboratory-confirmed COVID-19 should contact the study staff at their earliest convenience to report the event. Contact with the study staff could also be made by the participant's legal representative if the participant does not have the capacity to do so.

Any participant who has laboratory-confirmed asymptomatic SARS-CoV-2 infection, if occurred, should also follow the procedures outlined in the applicable local guideline. The participant should also contact the study staff at their earliest convenience to report the event.

Laboratory-confirmed symptomatic COVID-19 and asymptomatic SARS-CoV-2 infection will be reported as an AE and recorded on the CRF.

Any participant who has laboratory confirmed symptomatic COVID-19 or asymptomatic SARS-CoV-2 infection while participating in the study will discontinue study intervention. They may remain in the study, if deemed appropriate by the investigator, to complete all scheduled visits and assessments as described in the SoA (Section 1.3). As much information as possible should be collected from the participant as appropriate and recorded on the CRF.

8.5. Biological Samples

An overview of the timepoint and volume of blood samples that will be collected for immunogenicity evaluation, clinical safety laboratory evaluations, immunology, and serology is presented in Table 8.5 below.

Table 8.5 Timepoint and Maximum Blood Draw Volume Per Participant

Purpose of Sample Collection	Number of Scheduled Timepoints	Maximum Blood Draw Volume Per Participant Per Timepoint
Screening laboratory safety tests (including hematology, biochemistry, immunology, serology)	1	20 mL
Immunogenicity (anti-SARS-CoV-2 neutralizing antibody, antigen specific antibody)	6	20 mL
Maximum total blood draw volume		140 mL
Maximum daily blood draw volume		20 mL
Maximum blood draw volume within 28 days		60 mL

Note: repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Urine samples will be collected for urine pregnancy tests at the designated timepoints (see SoA, Section 1.3).

8.6. Pharmacokinetics

Pharmacokinetics are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Health Economics

Health economics are not evaluated in this study.

9. Statistical Considerations

The statistical analysis plan (SAP) will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section provides a summary of the statistical analysis for all study endpoints. A separate interim SAP may be prepared to provide a detailed description of the interim analysis, if necessary.

9.1. Statistical Hypotheses

The primary objective of this study is to demonstrate that MVC-COV1901 is superior to AZD1222 in terms of the GMT ratio of neutralizing antibody at 14 days after the second dose of study intervention (Visit 4/Day 43). Thus, the hypothesis to be tested in relation to the primary endpoint is as follows:

H_0: The $GMT_{MVC\text{-}COV1901}/GMT_{AZD1222}$ ratio of neutralizing antibody is ≤ 1 on Day 43.

H_1: The $GMT_{MVC\text{-}COV1901}/GMT_{AZD1222}$ ratio of neutralizing antibody is > 1 on Day 43.

If the lower bound of the two-sided 95% CI of the $GMT_{MVC\text{-}COV1901}/GMT_{AZD1222}$ ratio of neutralizing antibody is > 1, the immunogenic superiority of the MVC-COV1901 compared to the active control AZD1222 at 14 days after the second vaccination will be demonstrated.

The second co-primary of this study is to demonstrate the immunogenic non-inferiority of MVC-COV1901 to AZD1222 in Seroconversion rate (SCR) of neutralizing antibody titers at 14 days after the second dose of study intervention. Thus, the hypothesis to be tested in relation to the second co-primary endpoint is as follows:

H_0: The $SCR_{MVC\text{-}COV1901}$-$SCR_{AZD1222} \geq -5\%$ on Day 43.

H_1: The $SCR_{MVC\text{-}COV1901}$-$SCR_{AZD1222} < -5\%$ on Day 43. on Day 43.

9.1.1. Multiplicity Adjustment

Not applicable.

9.2. Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

Analysis set	Description
Screened Participants	All participants who have provided informed consent, were assigned an identification number, and underwent the screening procedures.
Randomized Set	All participants who are assigned a randomization number, regardless of the participants' treatment status in the study.

Safety Set	All randomized participants who received at least one dose of study intervention. Participants will be analyzed according to the study intervention they actually received.
Immunogenicity Analysis Set	All randomized participants who received 2 doses of study intervention, have a valid immunogenicity result prior to the first dose of study intervention and have at least one valid immunogenicity result at Visit 4. Participants will be analyzed according to the study intervention they actually received.
Per Protocol Immunogenicity (PPI) Analysis Set	All randomized participants who received 2 doses of study intervention within the pre-defined window, have a valid immunogenicity result prior to the first dose of study intervention and a valid immunogenicity result at Visit 4, and who do not have a major protocol deviation that is judged to impact the critical or key study data. Detailed criteria defining this analysis set will be determined prior to database lock and unblinding, and documented in the SAP. Participants will be analyzed according to the study intervention they actually received.
Full Analysis Set (FAS)	All randomized participants who received at least one dose of study intervention, irrespective of their protocol adherence and continued participation in the study. Participants who withdraw consent to participate in the study will be included up to the date of their study withdrawal. Participants will be analyzed according to the study intervention to which they are randomly assigned.
Per protocol Set (PPS)	The PPS will be defined for each immunogenicity analysis time point. For each visit, it includes participants in the FAS who receive the planned dose of randomized study intervention, and, up till the corresponding visit, no laboratory-confirmed COVID-19 infection, negative for SARS-CoV-2 anti-N tests, and have no major protocol deviation that is judged to impact the critical immunogenicity data. Detailed criteria defining this analysis set will be determined prior to database lock and unblinding, and documented in the SAP. Participants will be analyzed according to the study intervention to which they are randomly assigned.

9.3. Statistical Analyses

9.3.1. General Considerations

All measured variables and derived parameters will be listed by participant and summarized by descriptive statistics. Summary descriptive statistics will be provided for demographic/baseline

characteristics, secondary immunogenicity, safety, exploratory immunogenicity and efficacy variables. Data of all study sites will be pooled for statistical analysis. In general, tabulation of results will be displayed by treatment group and by visit.

Continuous variables will be summarized descriptively with number of participants, mean, median, standard deviation (SD), interquartile range (IQR), range (minimum and maximum), and 95% CI of mean and median (when appropriate). Categorical variables will be summarized with number and percentage of participants.

For all endpoint measurements, the last non-missing values before the first administration of study intervention will be used as baseline. Missing values will be regarded as missing. No imputation method will be applied for missing data transformation. Analyses will be performed using the available data points. For antibody titers lower than the lower limit of detection (LoD), the value will be replaced by half of the LoD. Values that were greater than the upper limit of quantification (ULOQ) were converted to the ULOQ.

Protocol deviations, including what generally constitutes major (important) or minor protocol deviations, are detailed in the SAP in accordance with ICH guidelines. All protocol deviations will be reviewed and classified as either important or minor by the clinical team. Protocol deviations will be reported according to the SOPs of the Sponsor or delegate.

9.3.2. Primary Immunogenicity Endpoint/Primary Estimand Analysis

The primary immunogenicity endpoint will be analyzed primarily on the Immunogenicity Analysis Set. The same analysis will also be performed on the PPI Analysis Set.

Refer to Section 9.1 for the statistical hypothesis to be tested in relation to the primary estimand. The types of intercurrent events for the primary estimand are provided in Table 9.1 below.

Table 9.1 Types of Intercurrent Events for the Primary Estimand

Intercurrent event	**Comment**
Not receiving the second dose of study intervention/missed dose	Participants will be excluded from the Immunogenicity Analysis Set and the PPI Analysis Set
Withdrawal from the study before the timepoint of primary endpoint assessment	Missing data will not be imputed. Participants will be excluded from the Immunogenicity Analysis Set and the PPI Analysis Set.

The primary immunogenicity endpoint includes the calculation of GMT and GMT ratio of neutralizing antibody titers at Visit 4/Day 43 (14 days after second dose of study intervention).

GMT is the geometric mean of the antibody titers. GMT ratio is defined as geometric mean of fold increase of post-study intervention titers over the baseline titers. The GMT of neutralizing antibody of all participants in each treatment group and the respective GMT ratio will be calculated as follows:

GMT = $\ln^{-1}(\frac{\sum_{i=1}^{n} lnX}{n})$, where X: antibody titer

GMT ratio = $\frac{GMT_{MVC-COV1901}}{GMT_{AZD1222}}$

Between-Treatment (MVC-COV1901 v.s. AZD1222) Immunogenicity Analysis:

The GMT and GMT ratio will be presented with two-sided 95% CI. Log_e-transformed antibody titer, ln(X), will be analyzed by using two-sample t test. The difference in the means on the natural log scale will be MVC-COV1901 minus AZD1222. The CI of GMT and GMT ratio will be calculated by the exponential of CI of the mean ln(X) and the CI of mean ln(X) difference, respectively. Kolmogorov-Smirnov method will be used to test whether data meet the assumption of normality. In case where normality assumption of ln(X) is not valid, additional GMT and GMT ratio and 95% CI estimated from the median of ln(X) will also be presented. Superiority will be declared if the lower bound of the two-sided 95% CI for the GMT ratio is greater than 1.

SCR is defined as the percentage of participants with at least 4-fold increase of post-study intervention antibody titers from baseline or from half of the the LoD if undetectable at baseline. SCR will be compared between treatments by using Cochran-Mantel-Haenszel test stratified by age group, chi-square or Fisher's exact test, and 95% CI of SCR treatment difference will be presented in normal approximation. Logistic regression may be applied with treatment odds ratio and it's 95% CI presented when there are other statistically significant baseline factors.

Sensitivity analysis by using analysis of covariates (ANCOVA) will be performed for the primary immunogenicity endpoint by adjusting for the covariates of site, , comorbidity, BMI, human immunodeficiency virus (HIV) status, and baseline serostatus of anti-SARS-CoV-2 neutralizing antibody, if appropriate.

The primary immunogenicity endpoint will be analyzed in the planned interim analysis only and will not be repeated in the final analysis at study end.

9.3.3. Primary Safety Endpoints

The primary safety endpoints will be analyzed on the Safety Set.

The primary safety endpoints include the occurrence of solicited (local and systemic) AEs, unsolicited AEs, MAAE, AESI, VAED, and SAE from Visit 2/Day 1 to Visit 5/Day 57 (28 days after second dose of study intervention).

Treatment emergent adverse events (TEAEs) will be summarized for the safety endpoints. A TEAE is an event that emerges after the first dose of study intervention having been absent before the administration of study intervention or worsens in intensity relative to the state before the first dose of study intervention.

Solicited AEs after the first and second dose of study intervention, and the overall occurrence after any dose of study intervention will be summarized. Solicited AEs will be further summarized by the reaction type (local or systemic) and the pre-specified AEs. For unsolicited AEs, the overall occurrence after any dose of study intervention will be summarized.

All AEs, including solicited AEs that fulfill the definition of SAE or MAAE, will be coded as system organ class (SOC) and preferred term (PT) using the most updated Medical Dictionary for Regulatory Activities (MedDRA) version. The number of events, number and percentage of participants will be summarized for each category of AEs. An overview of AEs with the number of events, number and percentage of participants who experience MAAE, related MAAE, AESI, VAED, SAE, related SAE, AE leading to discontinuation of study intervention, AE leading to study withdrawal, and death will be summarized for each treatment group and the total participants. The 95% CI of the percentage of participants will additionally be calculated in the summary of the overview of AEs.

The intensity and causality of AEs will be summarized for each treatment group and the total participants.

The primary safety endpoint will be analyzed in the planned interim analysis only and will not be repeated in the final analysis at study end.

9.3.4. Secondary Immunogenicity Endpoint Analysis

The secondary immunogenicity endpoint will be analyzed primarily on the Immunogenicity Analysis Set. The same analysis will also be performed on the PPI Analysis Set.

The GMT and GMT ratio of antigen-specific immunoglobulinwill be calculated as described in Section 9.3.2.

SCR is defined as the percentage of participants with at least 4-fold increase of post-study intervention antibody titers from baseline or from half of the LoD if undetectable at baseline. The number and percentage of participants with seroconversion in neutralizing antibody titers from baseline will be summarized. Chi-square will be used to compare the two treatment groups with a 95% CI, except for the case of small cell count (less than 5) where Fisher's exact test will be performed.

9.3.5. Secondary Safety Endpoints Analysis

The secondary safety endpoints will be analyzed on the Safety Set.

The secondary safety endpoints include the occurrence of MAAE, AESI, VAED, and SAE over the entire study period.

TEAEs will be summarized for the safety endpoints. All AEs will be coded as SOC and PT using the most updated MedDRA version. The number of events, number and percentage of participants will be summarized for each category of AEs. An overview of AEs with the number of events, number and percentage of participants who experience MAAE, related MAAE, AESI, VAED, SAE, related SAE, AE leading to discontinuation of study intervention, AE leading to

study withdrawal, and death will be summarized for each treatment group and the total participants. The 95% CI of the percentage of participants will additionally be calculated in the summary of the overview of AEs.

The intensity and causality of AEs will be summarized for each treatment group and the total participants.

9.3.6. Exploratory Endpoints Analyses

9.3.6.1. Antigen specific immunglobulin Titers

The exploratory immunogenicity endpoint will be analyzed primarily on the Immunogenicity Analysis Set. The same analysis will also be performed on the PPI Analysis Set.

The GMT and GMT ratio of antigen specific antibody will be calculated as described in Section 9.3.2.

For SCR, the number and percentage of participants with seroconversion in antigen specific antibody titers from baseline will be summarized. Chi-square will be used to compare the two treatment groups with a 95% CI, except for the case of small cell count (less than 5) where Fisher's exact test will be performed.

9.3.6.2. Efficacy Analysis

The exploratory efficacy endpoint will be analyzed primarily on the PPS. The same analysis will also be performed on the FAS.

The incidence per 1000 person-years of laboratory confirmed symptomatic COVID-19 cases (all cases and severe cases) occurring from ≥ 15 days after administration of each dose of study intervention will be summarized. The incidence per 1000 person-years of all laboratory-confirmed cases, including symptomatic COVID-19 and asymptomatic SARS-CoV-2 infection, occurring from ≥ 15 days after administration of each dose of study intervention will also be summarized.

9.3.7. Subgroup Analyses

Subgroup analysis by age, comorbidity, BMI, baseline HIV status, and baseline serostatus of anti-SARS-CoV-2 neutralizing antibody will be performed for the primary immunogenicity. Subgroup analysis by age group will be performed for the safety endpoints.

Other subgroup analyses deemed relevant by the regulatory authority may also be performed, and details will be provided in the SAP. Further details of the statistical considerations, analysis method, and analysis sets for the subgroup analysis will be provided in the SAP.

9.4. Interim Analysis

One interim analysis is planned in the study after all participants have completed Visit 5/Day 57 assessment. The primary and secondary immunogenicity and safety endpoints, as well as the exploratory immunogenicity endpoint of antigen specific antibody titers will be analyzed in the

interim analysis. The analysis of the exploratory efficacy endpoint will not be included in the interim analysis. The results of the interim analysis will be submitted to DINAVISA for evaluation and regulatory decision making to comply with local requirements.

The interim analysis will be conducted such that the ongoing study integrity is maintained. Only the independent study team, who is responsible for providing the interim analysis results to the Sponsor will be unblinded to the individual treatment group assignments. All other parties, ie, participants, investigators, the site personnel and the Sponsor staff who are involved in the blinded conduct of the study will remain blinded to study intervention until after the final database lock.

The planned interim analyses will be described in greater detail in the SAP or if needed, in a separate interim SAP.

9.5. Sample Size Determination

At least 942 participants will be randomized to receive study intervention.

The sample size calculation is based on the primary immunogenicity endpoint to establish immunogenic superiority of MVC-COV1901 to AZD1222 in terms of GMT ratio of neutralizing antibody at 14 days after the second dose of study intervention. The calculation is based on the following assumptions:

- Level of significance = 0.025 (one-sided)
- Level of power = 0.9
- Expected geometric mean ratio of MVC-COV1901 to AZD1222 = 1.2
- SD of natural log logarithm data = 0.81 (Reference: Phase II CT-COV-21 study, Day 57, MVC-COV1901, immunogenicity subset, N = 913)

Under the above assumptions, with the SD of 0.81 and expected GMT ratio of 1.2 (MVC-COV1901 to AZD1222), a sample size of 417 participants per treatment group will provide a power of 90% to declare immunogenic superiority of MVC-COV1901 to AZD1222 in terms of GMT ratio of neutralizing antibody titers at Visit 4/Day 43 (14 days after second dose of study intervention). Considering a 11.4% dropout rate, a total of at least 942 participants will be randomized in the study

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
    - Applicable ICH Good Clinical Practice (GCP) guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, investigator's brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
    - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

The financial disclosure information is provided in a separate document.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant or their legally authorized representative and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.

- A copy of the ICF(s) must be provided to the participant or their legally authorized representative.

- A participant who is rescreened is not required to sign a new ICF if the rescreening occurs within 28 days from the previous ICF signature date.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent

- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

Participant safety will be continuously monitored by the Sponsor's or delegate's safety review to detect safety signal at any time during the study. An IDMC will review the cumulative SAEs and other relevant safety data monthly and make appropriate recommendations to the Sponsor based

on the available data. Details of the IDMC meeting and the committee are provided separately in an IDMC charter.

The IDMC is a group of independent experts who are appointed to provide oversight and to ensure safe and ethical conduct of the study. The composition of the committee is dependent upon the scientific or medical skills and knowledge required for monitoring the study.

10.1.6. Dissemination of Clinical Study Data

All materials, documents and information supplied by the Sponsor or delegate to the investigator, and all materials, documents and information prepared or developed in the course of the study to be performed under this protocol, shall be the sole and exclusive property of the Sponsor.

The Sponsor or delegate will ensure that a final report on the study is prepared. The investigator will be required to sign a statement in the clinical study report that he/she confirms that, to the best of his/her knowledge, it accurately describes the conduct and results of the study.

As required by local regulation or by the IRB/IEC, a summary of the clinical study will be submitted by the Sponsor or delegate to the regulatory authorities and by the Sponsor or delegate or investigator to the IRB/IEC. Clinical study results will be publicly disclosed according to local requirements for reporting and public disclosure.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or eCRFs unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

- The Sponsor or delegate is responsible for the data management of this study, including quality checking of the data.

- The Sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 2 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9. Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the first participant is recruited in the clinical study.

Study/Site Termination

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines

- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator

- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 10.1 will be performed by the local laboratory.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 10.1 Protocol-required Clinical Safety Laboratory Tests

Hematology:	Hemoglobin (Hb), Red blood cell (RBC), Hematocrit (Hct), Mean corpuscular volume (MCV), Mean corpuscular hemoglobin (MCH), Mean corpuscular hemoglobin concentration (MCHC), Reticulocyte, White blood cell (WBC), Differential of leukocytes, Platelets, Prothrombin time, and Activated partial thromboplastin time (APTT)
Biochemistry:	Hemoglobin A1c (HbA1c), Blood urea nitrogen (BUN), Creatinine (Cr), Alanine transferase (ALT), and Aspartate aminotransferase (AST)
Immunology	Antinuclear antibody (ANA)
Serology	Anti-HIV antibody or rapid test, Anti-SARS-CoV-2 antibody rapid test

Investigators must document their review of each laboratory safety report.

10.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.
Definition of Solicited and Unsolicited AE
• Solicited AEs are predefined local (at the injection site) and systemic events for which the participant is specifically questioned, and which are noted by the participant in the participant diary. In this study, solicited AEs are predefined events occurring within 7 days after each dose of study intervention. • An unsolicited adverse event is an adverse event that is not solicited and is recorded using a participant diary. Unsolicited AEs include serious and nonserious Aes. In this study, unsolicited Aes are events occurring within 28 days after each dose of study intervention. • Potential unsolicited Aes may be medically attended (ie, symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a healthcare provider). The participant/legally authorized representative will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant/legally authorized representative concern. Detailed information about reported unsolicited Aes will be collected by qualified site personnel and documented in the participant's records. • Solicited and unsolicited Aes will be reviewed by the study staff and documented in the participant's records.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry) or other safety assessments (eg, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease)

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

a. Results in death

b. Is life threatening

The term *life threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.

- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

    - Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention abuse.

10.3.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

- The investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor or delegate in lieu of completion of the AE/SAE required form.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor or delegate. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor or delegate.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor or delegate to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the Sponsor or delegate within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to the Sponsor or Delegate via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the Sponsor or delegate will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.

- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section).

- Contacts for SAE reporting can be found in the Safety Management Plan or similar document.

SAE Reporting to the Sponsor or Delegate via Paper Data Collection Tool

- If the electronic data collection tool is not available, facsimile transmission of the SAE paper data collection tool should be used to transmit this information to the safety specialist designated by the Sponsor or delegate within 24 hours.

- Contacts for SAE reporting can be found in the Safety Management Plan or similar document.

10.4. Appendix 4: Adverse Events of Special Interest

Each participant will be assessed for immune-mediated AESIs during the study. The list is not intended to be exhaustive, nor to exclude other diagnoses potential to be AESI.

Categories	**Diagnoses**
Gastrointestinal disorders	• Celiac disease • Crohn's disease • Ulcerative colitis • Ulcerative proctitis
Liver disorders	• Autoimmune cholangitis • Autoimmune hepatitis • Primary biliary cirrhosis • Primary sclerosing cholangitis
Metabolic diseases	• Addison's disease • Autoimmune thyroiditis (including Hashimoto thyroiditis) • Diabetes mellitus type 1 • Grave's or Basedow's disease
Musculoskeletal disorders	• Antisynthetase syndrome • Dermatomyositis • Juvenile chronic arthritis (including Still's disease) • Mixed connective tissue disorder • Polymyalgia rheumatica • Polymyositis • Psoriatic arthropathy • Relapsing polychondritis • Rheumatoid arthritis • Scleroderma, including diffuse systemic form and CREST syndrome • Spondyloarthritis, including ankylosing spondylitis, reactive arthritis (Reiter's Syndrome) and undifferentiated spondyloarthritis • Systemic lupus erythematosus • Systemic sclerosis
Neuroinflammatory disorders	• Acute disseminated encephalomyelitis, including site specific variants: e.g., non-infectious encephalitis, encephalomyelitis, myelitis, radiculomyelitis • Cranial nerve disorders, including paralyses/paresis (e.g. Bell's palsy) • Guillain-Barré syndrome, including Miller Fisher syndrome and other variants • Tolosa Hunt syndrome • Immune-mediated peripheral neuropathies and plexopathies (including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy) • Multiple sclerosis

Categories	**Diagnoses**
	• Narcolepsy • Optic neuritis • Transverse Myelitis • Generalized convulsion*
Skin disorders	• Alopecia areata • Autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis) • Cutaneous lupus erythematosus • Erythema nodosum • Morphoea • Lichen planus • Psoriasis • Sweet's syndrome • Vitiligo
Vasculitides	• Large vessels vasculitis including giant cell arteritis such as Takayasu's arteritis and temporal arteritis • Medium sized and/or small vessels vasculitis including: polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg-Strauss syndrome (allergic granulomatous angiitis), Buerger's disease (thromboangiitis obliterans),necrotizing vasculitis and anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified), Henoch-Schonlein purpura, Behcet's syndrome, leukocytoclastic vasculitis
Others	• Antiphospholipid syndrome • Autoimmune hemolytic anemia • Autoimmune glomerulonephritis (including Immunoglobulin A nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis • Autoimmune myocarditis/cardiomyopathy • Autoimmune thrombocytopenia* • Goodpasture syndrome • Idiopathic pulmonary fibrosis • Pernicious anemia • Raynaud's phenomenon • Sarcoidosis • Sjögren's syndrome • Stevens-Johnson syndrome • Uveitis • Anaphylaxis* • Vasculitides*

* AESIs which have been proven to associate with vaccine that could theoretically be true for novel COVID-19 vaccines (SPEAC December 2020)

Source: Hyer et al. 2018

10.5. Appendix 5: Vaccine-associated Enhanced Diseases

Each participant will be assessed for these potential VAED relevant to COVID-19 vaccine during the study. To be recorded as VAED relevant to COVID-19, the subjects should be laboratory confirmed cases of COVID-19. The list is not intended to be exhaustive, nor to exclude other diagnoses potential to be VAED.

Body System	**Potential vaccine-associated enhanced disease**
Cardiac	• Myocarditis • Acute cardiac injury • STEMI • Arrhythmia • Heart failure • Endothelial dysfunction • Acute coronary syndrome • Takotsubo stress cardiomyopathy • Myocardial infarction
Neurologic	• Anosmia/Ageusia • Guillain Barré Syndrome • Encephalitis • Encephalopathy • Brain hemorrhage • Seizure • Acute disseminated encephalomyelitis (ADEM) • Myelitis • Aseptic meningitis
Hematologic	• Thrombosis • Stroke • Coagulopathy • Pulmonary embolus • Thrombocytopenia • Ischemia • Endothelial dysfunction(4)
Dermatologic	• Chilblain • Cutaneous vasculitis • Erythema multiforme • Alopecia
Gastrointestinal	• Ischemia/thrombosis
Liver	• Acute liver injury
Kidney	• Acute kidney injury
Multisystem Inflammatory Syndrome	• Multisystem inflammatory syndrome in children

Source: SPEAC December 2020

Detection of VAEDs

The investigator must proactively collect the result of pathogen (SARS-CoV-2) isolation or molecular biological test for viral (SARS-CoV-2) RNA in his/her best capacity.

For VAED meeting the criteria of an SAE, the investigator must take VAED into consideration simultaneously upon reporting SAE (by selecting the checkbox of the VAED item shown in the SAE reporting form as shown below), and proactively seek to include or exclude VAED based on the result, ie, positive or negative, of the pathogen (SARS-CoV-2) isolation or molecular biological test for viral (SARS-CoV-2) RNA.

The medical monitor of the study will also send relevant queries to the site if the result of the pathogen (SARS-CoV-2) isolation or molecular biological test for viral (SARS-CoV-2) RNA is not provided when the reported SAE is an AE listed in the list above for VAED, community acquired pneumonia, encephalitis, myocarditis, or neuropathy.

1. GENERAL INFORMATION		
PROTOCOL No.: CT-COV-31	COUNTRY:	SITE ID:
☐ SAE	☐ AESI, ……	☐ VAED, ……

10.6. Appendix 6: Country-specific Requirements

10.6.1. Listing of investigators

Principal investigators

Prof. Dr. Laurentino Ramón Barrios Monges

Prof. Dr. Luis Francisco Armoa García

Prof. Dr. Julio Cesar Torales Benítez

Investigators responsible site Central – Hospital de Clínicas San Lorenzo

Prof. Dr. Luis Francisco Armoa García

Prof. Dr. Julio Cesar Torales Benítez

Investigators responsible site de Sede Alto Paraná – Hospital Fundación Tesãi

Dr. Fernando Bittinger Rolón

Dr. Federico Augusto Lacarrubba Codas

10.6.2. Study Sites

This study is designed to be carried out with participants in 2 different sites called headquarters, in the South American region, both located in the Republic of Paraguay, being chosen as sites on 1. Hospital de Clínicas in the city of San Lorenzo, Central Department and 2. the Tesai Foundation Hospital located in the city called Ciudad del Este, in the department of Alto Paraná. Participants will go to one of these sites according to their preference for the 7 visits documented in the protocol

10.6.3. Insurance of emergency.

The participants of this research study, will have an insurance of emergency medical care in case they require it during the entire period of study, it is determined that it will be at Home or in care centers determined by the insurer or virtual consultation, where they can receive medical attention or in case of need, transfer to a medical care center in each headquarters that would be the Hospital of Clinics in the department Central and the Hospital Foundation Tesai in the department of Alto Paraná. This medical care will be provided by EME ambulance services in both regions. (in

10.6.4. Life insurance policy

The participants of this study will have a life insurance policy provided by the company called La Consolidada de Seguros S.A, which will be valid for a period of 12 months from the

beginning of the study intervention. (in Annex: contract with the company for the provision of the service)

10.6.5. Storage and distribution of vaccines in Paraguay

The safekeeping, storage and distribution of vaccines to both research centers will be in charge of the company La Policlinic S.A., a leading distribution company in this type of services in Paraguay. The vaccines shall be kept in the warehouses of that undertaking and distributed to the research centers on a daily basis, with appropriate transport measures, according to the doses required and requested from the undertaking by the researchers. Once delivered to each headquarters will be sheltered in refrigerators in order to maintain the temperature of 2 to 8 degrees as required by their specifications both types of vaccines thus avoiding the loss of cold chain.

10.6.6. Justification for importing vaccines

Import of 2000 doses of MVC 1901 vaccine was made, since according to the handling protocol and the technical specifications of the vaccine once the vial is opened, it must be used within 4 hours, in case the time is exceeded for any reason, the vial must be discarded following the manufacturer's recommendations. Or for any other eventuality that may occur, such as rupture of the vial or any other eventuality that could occur so that the Clinical Study is not affected or delayed. In the event that there is a remainder, it will be made available to the health authorities

10.6.7. Sponsor data in Paraguay

The legal representative in Paraguay is the Horvath Laboratory of Gabriela de los Angeles Horvath Candia, located at Eligio Ayala #1470, Asunción - Paraguay.

10.7. Appendix 7: World Health Organization (WHO) COVID-19 Case Definitions

Suspected case of SARS-CoV-2 infection

A. A person who meets the clinical AND epidemiological criteria:
Clinical Criteria:
- Acute onset of fever AND cough; OR
- Acute onset of ANY THREE OR MORE of the following signs or symptoms: Fever, cough, general weakness/fatigue[1], headache, myalgia, sore throat, coryza, dyspnoea, anorexia/nausea/vomiting[1], diarrhoea, altered mental status

AND

Epidemiological Criteria:
- Residing or working in an area with high risk of transmission of virus: closed residential settings, humanitarian settings such as camp and camp-like settings for displaced persons; anytime within the 14 days prior to symptom onset; or
- Residing or travel to an area with community transmission anytime within the 14 days prior to symptom onset; or
- Working in any health care setting, including within health facilities or within the community; any time within the 14 days prior of symptom onset.

B. A patient with severe acute respiratory illness:
(SARI: acute respiratory infection with history of fever or measured fever of ≥ 38 C°; and cough; with onset within the last 10 days; and requires hospitalization)
C. Asymptomatic person not meeting epidemiologic criteria with a positive SARS-CoV-2 Antigen-RDT[2]

Probable case of SARS-CoV-2 infection

A. A patient who meets clinical criteria above AND is a contact of a probable or confirmed case, or linked to a COVID-19 cluster[3]
B. A suspect case with chest imaging showing findings suggestive of COVID-19 disease[4]
C. A person with recent onset of anosmia (loss of smell) or ageusia (loss of taste) in the absence of any other identified cause.
D. Death, not otherwise explained, in an adult with respiratory distress preceding death AND was a contact of a probable or confirmed case or linked to a COVID-19 cluster[3]

Confirmed case of SARS-CoV-2 infection

A. A person with a positive Nucleic Acid Amplification Test (NAAT)
B. A person with a positive SARS-CoV-2 Antigen-RDT AND meeting either the probable case definition or suspect criteria A OR B

C. An asymptomatic person with a positive SARS-CoV-2 Antigen-RDT who is a contact of a probable or confirmed case

[1] Signs separated with slash (/) are to be counted as one sign.

[2] NAAT is required for confirmation

[3] A group of symptomatic individuals linked by time, geographic location and common exposures, containing at least one NAAT-confirmed case or at least two epidemiologically linked, symptomatic (meeting clinical criteria of Suspect case definition A or B) persons with positive AgRDTs (based on ≥ 97% specificity of test and desired >99.9% probability of at least one positive result being a true positive)

[4] Typical chest imaging findings suggestive of COVID-19 include the following:

- Chest radiography: hazy opacities, often rounded in morphology, with peripheral and lower lung distribution
- Chest CT: multiple bilateral ground glass opacities, often rounded in morphology, with peripheral and lower lung distribution
- Lung ultrasound: thickened pleural lines, B lines (multifocal, discrete, or confluent), consolidative patterns with or without air bronchograms.

Source: WHO COVID-19: Case Definition. Updated in Public health surveillance for COVID-19, published 16 December 2020. Available at https://www.who.int/publications/i/item/WHO-2019-nCoV-Surveillance_Case_Definition-2020.2

10.8. Appendix 8: Abbreviations

ACE2	Angiotensin-converting enzyme 2
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse events of special interest
$Al(OH)_3$	Aluminum hydroxide
BMI	Body Mass Index
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus Disease 2019
CpG	Cytosine phosphoguanine
CMA	Conditional Marketing Authorization
CRF	Case report form
DNA	Deoxyribonucleic acid
eCRF	Electronic Case Report Forms
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOS	End of study
ET	Early termination
EUA	Emergency Use Authorization
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GMT	Geometric mean titers
HbA1c	Hemoglobin A1c
hCG	Human chorionic gonadotropin
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IEC	Independent ethics committees
IFN	Interferon
IL	Interleukin
IM	Intramuscular
IMP	Investigational medicinal product
IRB	Institutional Review Board
IQR	Interquartile range
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LoD	Lower limit of detection
MAAE	Medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MERS-CoV	Middle East respiratory syndrome coronavirus
mRNA	Messenger ribonucleic acid

NIMP	Non-investigational medicinal product
ODN	Oligodeoxynucleotide
pDCs	Plasmacytoid dendritic cells
PIC/S	Pharmaceutical Inspection Co-operation Scheme
PPI	Per protocol Immunogenicity
PPS	Per protocol Set
PT	Preferred term
RBD	Receptor binding domain
RT-PCR	Reverse transcription polymerase chain reaction
S protein	Spike protein
SAE	Serious adverse events
SARS-CoV	Severe acute respiratory syndrome coronavirus
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAP	Statistical Analysis Plan
SCR	Seroconversion rate
SD	Standard deviation
SoA	Schedule of activities
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected unexpected serious adverse reactions
TCID50	Fifty-percent tissue culture infective dose
TEAE	Treatment emergent adverse events
Th1	T helper type 1
TNF	Tumor necrosis factor
ULOQ	Upper limit of quantification
US	United States
VAED	Vaccine-associated enhanced disease

10.9. Appendix 9: Glossary of Terms on Clinical Trials

TERM	DEFINITION
Blinding	One or more parties of the clinical trial are kept unaware of the treatment assignment. Patients, investigators, and health care providers may all be blinded to the treatment a patient is receiving.
Clinical Significance	Change in a subject's clinical condition regarded as important whether or not due to the test intervention.
Compliance (in relation to clinical trials)	Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
Confidentiality	Prevention of disclosure to others than authorized individuals of a sponsor's proprietary information or of a subject's identity.
Informed Consent Form	Informed consent is a process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
Independent Data Monitoring Committee (IDMC)	An independent committee that may be established by the sponsor to assess, at intervals, the progress of a clinical investigation, the safety data, or the critical performance endpoints and make recommendations to the sponsor whether to continue, modify, or stop an investigation.
Endpoint	Principal indicator(s) used for assessing the primary question (i.e., hypothesis) of a clinical trial. A variable that pertains to the efficacy or safety evaluations of a trial. An endpoint is more specific as compared to an outcome since it relate to the planned objective of the study.
Enrollment	The process of registering or entering a patient into a clinical trial. Once a patient has been enrolled, the participant would then follow the clinical trial protocol. Clinical investigations are designed to enroll a set number of participants to increase the likelihood of answering the trial questions.
Health Care Provider	One who directly or indirectly administers interventions that are designed to improve the physical or emotional status of patients. A person otherwise authorized or permitted by law to administer healthcare in the ordinary course of business or practice of a profession, including a healthcare facility.
Hypothesis	A testable statement regarding the investigational medical device safety or performance (effectiveness) that is used to design the clinical trial and that can be accepted or rejected based on the results of the clinical trial and statistical calculations.
Inclusion/ Exclusion Criteria	The medical or other guidelines that determines whether a person may or may not be allowed to enter a clinical trial. These criteria are based on such factors as age, gender, the type and stage of a disease, previous treatment history, and other medical conditions. The criteria are not used to reject people personally, but to

TERM	DEFINITION
	identify appropriate participants for the trial and keep them safe. Also known as Eligibility or Enrollment Criteria
Institutional Review Board (IRB)	Any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of, biomedical research involving human subjects. The primary purpose of such review is to assure the protection of the rights and welfare of the human subjects. Also known as Ethics Committee (EC).
Intervention	The diagnostic or therapeutic device, biologic, and/or drug under investigation in a clinical trial that is believed to have an effect on outcomes of interest in a study.
Investigator	A person responsible for the conduct of the clinical trial at the trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the Principal Investigator (PI).
Labeling	All text, tables, and figures in labeling as described in regulations for a specific product.
Legally Authorized Representative	Individual who is authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.
Lost to Follow Up	The act of concluding participation, prior to completion of all protocol-required elements, in a trial by an enrolled subject.
Multicenter Trial	A clinical trial conducted according to a single protocol but at more than one site, and, therefore, carried out by more than one investigator.
Outcome	Events or experiences that clinicians or investigators examining the impact of an intervention or exposure measure because they believe such events or experiences may be influenced by the research intervention or exposure. Outcome is more general than endpoint in that it does not necessarily relate to a planned objective of the study.
Protocol	A document that describes the objectives(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. A protocol amendment is a written description of a change(s) to or a formal change of a protocol.
Randomization	The process of assigning trial subjects to investigational treatment or control groups (may use a comparator) using an element of chance to determine the assignments in order to reduce bias.
Recruitment	Active efforts by investigators to identify subjects who may be suitable for enrollment into a clinical trial. Subjects are selected on the basis of the protocol's inclusion and exclusion criteria during the clinical trial recruitment period. The number of subjects that must be recruited for enrollment into a study and meet the requirements of the protocol. In multicenter studies, each

TERM	DEFINITION
	investigator has a recruitment target or defined number of subjects to be enrolled.
Safety	Safety is relative freedom from harm. In clinical trials, this refers to an absence of harmful side effects resulting from use of the product and may be assessed by laboratory testing of biological samples, special tests and procedures, psychiatric evaluation, and/or physical examination of subjects.
Screening (of subjects)	A process of active evaluation of potential participants for enrollment in a trial. After a patient is recruited, screening occurs during the enrollment period to see if they meet the inclusion and exclusion criteria. If they meet the criteria, the subject is eligible to enroll in the trial.
Sponsor	An individual, company, institution, or organization that takes responsibility for the initiation, management, and/or financing of a clinical trial.
Statistical Analysis Plan	A document detailing the methods of all planned analyses of the clinical study data.
Subject/ Participant	An individual who participates in a clinical trial either as a recipient of the investigational product(s) or as a control. The term "subject" is part of the federal regulation and may be used interchangeably with participant.
Termination	Discontinuance, by sponsor or by withdrawal of IRB or FDA approval, of a clinical trial before completion. This termination can be at a site or the entire study.

*The Terms and the Definitions provide in the above table are captured from "2017 Meeting Materials of the Patient Engagement Advisory Committee-Glossary of Terms on Clinical Trial." (Available at: https://www.fda.gov/media/108378/download; accessed on 5 Aug 2021)

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