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Supplementary appendix

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Table S1. WHO international standard reference panels from National Institute for Biological Standards and Control (NIBSC; Potters Bar, UK)

	Research Reagent	**WHO International Standard**	**WHO Reference Panel**					
NIBSC Code	NIBSC 20/130	NIBSC 20/136	NIBSC 20/268					
			High 20/150	Mid 20/148	low S, high N 20/144	Low 20/140	NC 20/142	
Contents	**0·1 mL** of frozen plasma	Freeze-dried equivalent of 0·25 mL pooled human plasma	Freeze-dried equivalent of 0·25 mL pooled human plasma	Freeze-dried equivalent of 0·25 mL pooled human plasma	Freeze-dried equivalent of 0·25 mL pooled human plasma	Freeze-dried equivalent of 0·25 mL pooled human plasma	Freeze-dried equivalent of 0·25 mL pooled human plasma	
Reconstitution	Thaw at ambient temperature	**0·25 mL** sterile distilled water	**0·25 mL** sterile distilled water	**0·25 mL** sterile distilled water	**0·25 mL** sterile distilled water	**0·25 mL** sterile distilled water	**0·25 mL** sterile distilled water	
Storage	-20 °C	-20 °C	-20 °C	-20 °C	-20 °C	-20 °C	-20 °C	
Neutralising Ab	**1300**	**1000**	**1473**	**210**	**95**	**44**	—	IU/mL
anti-Spike IgG	476	For binding antibody assays, an arbitrary unitage of **1000** binding antibody units (BAU)/mL can be used to assist the comparison of assays detecting the same class of immunoglobulins with the same specificity	832	241	86	53	—	BAU/mL

Table S2. The method for converting anti-Spike IgG GMT to WHO's BAU/mL

	Sample ID	titre endpoint	GMT
NIBSC 20/136	study sample1-1	14595	10960·9
	study sample1-2	11556	
	study sample1-3	10694	
	study sample1-4	9963	
	study sample1-5	11075	
	study sample1-6	10218	
	study sample1-7	9347	

Table S3. Solicited Adverse Events after the First Dosing

	All, n (%)			≥ 20 to < 65 years, n (%)			≥ 65 years, n (%)		
	MVC-COV1901 (N = 3295)	Placebo (N = 549)	Total (N = 3844)	MVC-COV1901 (N = 2575)	Placebo (N = 431)	Total (N = 3006)	MVC-COV1901 (N = 720)	Placebo (N = 118)	Total (N = 838)
Any Solicited Local AEs	2040 (61·9)	90 (16·4)	2130 (55·4)	1772 (68·8)	80 (18·6)	1852 (61·6)	268 (37·2)	10 (8·5)	278 (33·2)
Pain/Tenderness	2011 (61·0)	88 (16·0)	2099 (54·6)	1755 (68·2)	78 (18·1)	1833 (61·0)	256 (35·6)	10 (8·5)	266 (31·7)
Grade 1	1952 (59·2)	85 (15·5)	2037 (53·0)	1699 (66·0)	77 (17·9)	1776 (59·1)	253 (35·1)	8 (6·8)	261 (31·1)
Grade 2	51 (1·5)	3 (0·5)	54 (1·4)	48 (1·9)	1 (0·2)	49 (1·6)	3 (0·4)	2 (1·7)	5 (0·6)
Grade 3	8 (0·2)	0	8 (0·2)	8 (0·3)	0	8 (0·3)	0	0	0
Induration/Swelling	187 (5·7)	4 (0·7)	191 (5·0)	154 (6·0)	4 (0·9)	158 (5·3)	33 (4·6)	0	33 (3·9)
Grade 1	171 (5·2)	4 (0·7)	175 (4·6)	138 (5·4)	4 (0·9)	142 (4·7)	33 (4·6)	0	33 (3·9)
Grade 2	15 (0·5)	0	15 (0·4)	15 (0·6)	0	15 (0·5)	0	0	0
Grade 3	1 (<0·1)	0	1 (<0·1)	1 (<0·1)	0	1 (<0·1)	0	0	0
Erythema/Redness	80 (2·4)	0	80 (2·1)	66 (2·6)	0	66 (2·2)	14 (1·9)	0	14 (1·7)
Grade 1	78 (2·4)	0	78 (2·0)	64 (2·5)	0	64 (2·1)	14 (1·9)	0	14 (1·7)
Grade 2	2 (0·1)	0	2 (0·1)	2 (0·1)	0	2 (0·1)	0	0	0
Any Solicited Systemic AEs	1400 (42·5)	194 (35·3)	1594 (41·5)	1179 (45·8)	171 (39·7)	1350 (44·9)	221 (30·7)	23 (19·5)	244 (29·1)
Malaise/Fatigue	842 (25·6)	118 (21·5)	960 (25·0)	736 (28·6)	105 (24·4)	841 (28·0)	106 (14·7)	13 (11·0)	119 (14·2)
Grade 1	716 (21·7)	95 (17·3)	811 (21·1)	619 (24·0)	85 (19·7)	704 (23·4)	97 (13·5)	10 (8·5)	107 (12·8)

	All, n (%)			≥ 20 to < 65 years, n (%)			≥ 65 years, n (%)		
	MVC-COV1901 (N = 3295)	**Placebo (N = 549)**	**Total (N = 3844)**	**MVC-COV1901 (N = 2575)**	**Placebo (N = 431)**	**Total (N = 3006)**	**MVC-COV1901 (N = 720)**	**Placebo (N = 118)**	**Total (N = 838)**
Grade 2	114 (3·5)	21 (3·8)	135 (3·5)	106 (4·1)	18 (4·2)	124 (4·1)	8 (1·1)	3 (2·5)	11 (1·3)
Grade 3	12 (0·4)	2 (0·4)	14 (0·4)	11 (0·4)	2 (0·5)	13 (0·4)	1 (0·1)	0	1 (0·1)
Myalgia	655 (19·9)	66 (12·0)	721 (18·8)	552 (21·4)	57 (13·2)	609 (20·3)	103 (14·3)	9 (7·6)	112 (13·4)
Grade 1	574 (17·4)	62 (11·3)	636 (16·5)	478 (18·6)	54 (12·5)	532 (17·7)	96 (13·3)	8 (6·8)	104 (12·4)
Grade 2	72 (2·2)	4 (0·7)	76 (2·0)	65 (2·5)	3 (0·7)	68 (2·3)	7 (1·0)	1 (0·8)	8 (1·0)
Grade 3	9 (0·3)	0	9 (0·2)	9 (0·3)	0	9 (0·3)	0	0	0
Headache	496 (15·1)	75 (13·7)	571 (14·9)	432 (16·8)	65 (15·1)	497 (16·5)	64 (8·9)	10 (8·5)	74 (8·8)
Grade 1	442 (13·4)	65 (11·8)	507 (13·2)	379 (14·7)	56 (13·0)	435 (14·5)	63 (8·8)	9 (7·6)	72 (8·6)
Grade 2	49 (1·5)	10 (1·8)	59 (1·5)	48 (1·9)	9 (2·1)	57 (1·9)	1 (0·1)	1 (0·8)	2 (0·2)
Grade 3	5 (0·2)	0	5 (0·1)	5 (0·2)	0	5 (0·2)	0	0	0
Diarrhoea	355 (10·8)	52 (9·5)	407 (10·6)	302 (11·7)	47 (10·9)	349 (11·6)	53 (7·4)	5 (4·2)	58 (6·9)
Grade 1	309 (9·4)	41 (7·5)	350 (9·1)	263 (10·2)	38 (8·8)	301 (10·0)	46 (6·4)	3 (2·5)	49 (5·8)
Grade 2	39 (1·2)	10 (1·8)	49 (1·3)	32 (1·2)	8 (1·9)	40 (1·3)	7 (1·0)	2 (1·7)	9 (1·1)
Grade 3	7 (0·2)	1 (0·2)	8 (0·2)	7 (0·3)	1 (0·2)	8 (0·3)	0	0	0
Nausea/Vomiting	159 (4·8)	30 (5·5)	189 (4·9)	135 (5·2)	27 (6·3)	162 (5·4)	24 (3·3)	3 (2·5)	27 (3·2)
Grade 1	143 (4·3)	27 (4·9)	170 (4·4)	119 (4·6)	24 (5·6)	143 (4·8)	24 (3·3)	3 (2·5)	27 (3·2)
Grade 2	15 (0·5)	2 (0·4)	17 (0·4)	15 (0·6)	2 (0·5)	17 (0·6)	0	0	0

	All, n (%)			≥ 20 to < 65 years, n (%)			≥ 65 years, n (%)		
	MVC-COV1901 (N = 3295)	**Placebo (N = 549)**	**Total (N = 3844)**	**MVC-COV1901 (N = 2575)**	**Placebo (N = 431)**	**Total (N = 3006)**	**MVC-COV1901 (N = 720)**	**Placebo (N = 118)**	**Total (N = 838)**
Grade 3	1 (<0·1)	1 (0·2)	2 (0·1)	1 (<0·1)	1 (0·2)	2 (0·1)	0	0	0
Fever	**13 (0·4)**	**1 (0·2)**	**14 (0·4)**	**11 (0·4)**	**1 (0·2)**	**12 (0·4)**	**2 (0·3)**	**0**	**2 (0·2)**
Grade 1	8 (0·2)	1 (0·2)	9 (0·2)	7 (0·3)	1 (0·2)	8 (0·3)	1 (0·1)	0	1 (0·1)
Grade 2	3 (0·1)	0	3 (0·1)	3 (0·1)	0	3 (0·1)	0	0	0
Grade 3	1 (<0·1)	0	1 (<0·1)	1 (<0·1)	0	1 (<0·1)	0	0	0
Grade4	1 (<0·1)	0	1 (<0·1)	0	0	0	1 (0·1)	0	1 (0·1)

Table S4. Solicited Adverse Events after the Second Dosing

	All, n (%)			≥ 20 to < 65 years, n (%)			≥ 65 years, n (%)		
	MVC-COV1901 (N = 3295)	**Placebo (N = 549)**	**Total (N = 3844)**	**MVC-COV1901 (N = 2575)**	**Placebo (N = 431)**	**Total (N = 3006)**	**MVC-COV1901 (N = 720)**	**Placebo (N = 118)**	**Total (N = 838)**
Any Solicited Local AEs	1832 (55·6)	81 (14·8)	1913 (49·8)	1595 (61·9)	72 (16·7)	1667 (55·5)	237 (32·9)	9 (7·6)	246 (29·4)
Pain/Tenderness	1791 (54·4)	81 (14·8)	1872 (48·7)	1566 (60·8)	72 (16·7)	1638 (54·5)	225 (31·3)	9 (7·6)	234 (27·9)
Grade 1	1727 (52·4)	78 (14·2)	1805 (47·0)	1508 (58·6)	69 (16·0)	1577 (52·5)	219 (30·4)	9 (7·6)	228 (27·2)
Grade 2	59 (1·8)	2 (0·4)	61 (1·6)	54 (2·1)	2 (0·5)	56 (1·9)	5 (0·7)	0	5 (0·6)
Grade 3	5 (0·2)	1 (0·2)	6 (0·2)	4 (0·2)	1 (0·2)	5 (0·2)	1 (0·1)	0	1 (0·1)
Induration/Swelling	233 (7·1)	1 (0·2)	234 (6·1)	194 (7·5)	1 (0·2)	195 (6·5)	39 (5·4)	0	39 (4·7)
Grade 1	200 (6·1)	1 (0·2)	201 (5·2)	165 (6·4)	1 (0·2)	166 (5·5)	35 (4·9)	0	35 (4·2)
Grade 2	32 (1·0)	0	32 (0·8)	28 (1·1)	0	28 (0·9)	4 (0·6)	0	4 (0·5)
Grade 3	1 (<0·1)	0	1 (<0·1)	1 (<0·1)	0	1 (<0·1)	0	0	0
Erythema/Redness	98 (3·0)	0	98 (2·5)	85 (3·3)	0	85 (2·8)	13 (1·8)	0	13 (1·6)
Grade 1	94 (2·9)	0	94 (2·4)	81 (3·1)	0	81 (2·7)	13 (1·8)	0	13 (1·6)
Grade 2	4 (0·1)	0	4 (0·1)	4 (0·2)	0	4 (0·1)	0	0	0
Any Solicited Systemic AEs	1159 (35·2)	142 (25·9)	1301 (33·8)	986 (38·3)	123 (28·5)	1109 (36·9)	173 (24·0)	19 (16·1)	192 (22·9)
Malaise/Fatigue	788 (23·9)	91 (16·6)	879 (22·9)	705 (27·4)	80 (18·6)	785 (26·1)	83 (11·5)	11 (9·3)	94 (11·2)
Grade 1	656 (19·9)	76 (13·8)	732 (19·0)	587 (22·8)	67 (15·5)	654 (21·8)	69 (9·6)	9 (7·6)	78 (9·3)

	All, n (%)			≥ 20 to < 65 years, n (%)			≥ 65 years, n (%)		
	MVC-COV1901 (N = 3295)	**Placebo (N = 549)**	**Total (N = 3844)**	**MVC-COV1901 (N = 2575)**	**Placebo (N = 431)**	**Total (N = 3006)**	**MVC-COV1901 (N = 720)**	**Placebo (N = 118)**	**Total (N = 838)**
Grade 2	121 (3·7)	14 (2·6)	135 (3·5)	108 (4·2)	12 (2·8)	120 (4·0)	13 (1·8)	2 (1·7)	15 (1·8)
Grade 3	11 (0·3)	1 (0·2)	12 (0·3)	10 (0·4)	1 (0·2)	11 (0·4)	1 (0·1)	0	1 (0·1)
Myalgia	521 (15·8)	43 (7·8)	564 (14·7)	430 (16·7)	36 (8·4)	466 (15·5)	91 (12·6)	7 (5·9)	98 (11·7)
Grade 1	449 (13·6)	38 (6·9)	487 (12·7)	368 (14·3)	33 (7·7)	401 (13·3)	81 (11·3)	5 (4·2)	86 (10·3)
Grade 2	63 (1·9)	2 (0·4)	65 (1·7)	55 (2·1)	1 (0·2)	56 (1·9)	8 (1·1)	1 (0·8)	9 (1·1)
Grade 3	9 (0·3)	3 (0·5)	12 (0·3)	7 (0·3)	2 (0·5)	9 (0·3)	2 (0·3)	1 (0·8)	3 (0·4)
Headache	435 (13·2)	61 (11·1)	496 (12·9)	378 (14·7)	51 (11·8)	429 (14·3)	57 (7·9)	10 (8·5)	67 (8·0)
Grade 1	378 (11·5)	54 (9·8)	432 (11·2)	326 (12·7)	46 (10·7)	372 (12·4)	52 (7·2)	8 (6·8)	60 (7·2)
Grade 2	55 (1·7)	7 (1·3)	62 (1·6)	50 (1·9)	5 (1·2)	55 (1·8)	5 (0·7)	2 (1·7)	7 (0·8)
Grade 3	2 (0·1)	0	2 (0·1)	2 (0·1)	0	2 (0·1)	0	0	0
Diarrhoea	248 (7·5)	35 (6·4)	283 (7·4)	211 (8·2)	34 (7·9)	245 (8·2)	37 (5·1)	1 (0·8)	38 (4·5)
Grade 1	202 (6·1)	32 (5·8)	234 (6·1)	174 (6·8)	31 (7·2)	205 (6·8)	28 (3·9)	1 (0·8)	29 (3·5)
Grade 2	42 (1·3)	2 (0·4)	44 (1·1)	34 (1·3)	2 (0·5)	36 (1·2)	8 (1·1)	0	8 (1·0)
Grade 3	4 (0·1)	1 (0·2)	5 (0·1)	3 (0·1)	1 (0·2)	4 (0·1)	1 (0·1)	0	1 (0·1)
Nausea/Vomiting	126 (3·8)	13 (2·4)	139 (3·6)	110 (4·3)	12 (2·8)	122 (4·1)	16 (2·2)	1 (0·8)	17 (2·0)
Grade 1	112 (3·4)	12 (2·2)	124 (3·2)	97 (3·8)	11 (2·6)	108 (3·6)	15 (2·1)	1 (0·8)	16 (1·9)
Grade 2	13 (0·4)	1 (0·2)	14 (0·4)	12 (0·5)	1 (0·2)	13 (0·4)	1 (0·1)	0	1 (0·1)

	All, n (%)			≥ 20 to < 65 years, n (%)			≥ 65 years, n (%)		
	MVC-COV1901 (N = 3295)	**Placebo (N = 549)**	**Total (N = 3844)**	**MVC-COV1901 (N = 2575)**	**Placebo (N = 431)**	**Total (N = 3006)**	**MVC-COV1901 (N = 720)**	**Placebo (N = 118)**	**Total (N = 838)**
Grade 3	1 (<0·1)	0	1 (<0·1)	1 (<0·1)	0	1 (<0·1)	0	0	0
Fever	10 (0·3)	1 (0·2)	11 (0·3)	5 (0·2)	1 (0·2)	6 (0·2)	5 (0·7)	0	5 (0·6)
Grade 1	6 (0·2)	1 (0·2)	7 (0·2)	1 (<0·1)	1 (0·2)	2 (0·1)	5 (0·7)	0	5 (0·6)
Grade 2	3 (0·1)	0	3 (0·1)	3 (0·1)	0	3 (0·1)	0	0	0
Grade 3	1 (<0·1)	0	1 (<0·1)	1 (<0·1)	0	1 (<0·1)	0	0	0

Table S5. Solicited Adverse Events After any Dosing

	All, n (%)			≥ 20 to < 65 years, n (%)			≥ 65 years, n (%)		
	MVC-COV1901 (N = 3295)	**Placebo (N = 549)**	**Total (N = 3844)**	**MVC-COV1901 (N = 2575)**	**Placebo (N = 431)**	**Total (N = 3006)**	**MVC-COV1901 (N = 720)**	**Placebo (N = 118)**	**Total (N = 838)**
Any Solicited Local AEs	**2381 (72·3)**	**129 (23·5)**	**2510 (65·3)**	**2030 (78·8)**	**113 (26·2)**	**2143 (71·3)**	**351 (48·8)**	**16 (13·6)**	**367 (43·8)**
Pain/Tenderness	**2346 (71·2)**	**128 (23·3)**	**2474 (64·4)**	**2009 (78·0)**	**112 (26·0)**	**2121 (70·6)**	**337 (46·8)**	**16 (13·6)**	**353 (42·1)**
Grade 1	2237 (67·9)	123 (22·4)	2360 (61·4)	1907 (74·1)	109 (25·3)	2016 (67·1)	330 (45·8)	14 (11·9)	344 (41·1)
Grade 2	97 (2·9)	4 (0·7)	101 (2·6)	91 (3·5)	2 (0·5)	93 (3·1)	6 (0·8)	2 (1·7)	8 (1·0)
Grade 3	12 (0·4)	1 (0·2)	13 (0·3)	11 (0·4)	1 (0·2)	12 (0·4)	1 (0·1)	0	1 (0·1)
Induration/Swelling	**347 (10·5)**	**5 (0·9)**	**352 (9·2)**	**286 (11·1)**	**5 (1·2)**	**291 (9·7)**	**61 (8·5)**	**0**	**61 (7·3)**
Grade 1	303 (9·2)	5 (0·9)	308 (8·0)	246 (9·6)	5 (1·2)	251 (8·3)	57 (7·9)	0	57 (6·8)
Grade 2	42 (1·3)	0	42 (1·1)	38 (1·5)	0	38 (1·3)	4 (0·6)	0	4 (0·5)
Grade 3	2 (0·1)	0	2 (0·1)	2 (0·1)	0	2 (0·1)	0	0	0
Erythema/Redness	**161 (4·9)**	**0**	**161 (4·2)**	**138 (5·4)**	**0**	**138 (4·6)**	**23 (3·2)**	**0**	**23 (2·7)**
Grade 1	155 (4·7)	0	155 (4·0)	132 (5·1)	0	132 (4·4)	23 (3·2)	0	23 (2·7)
Grade 2	6 (0·2)	0	6 (0·2)	6 (0·2)	0	6 (0·2)	0	0	0
Any Solicited Systemic AEs	**1774 (53·8)**	**249 (45·4)**	**2023 (52·6)**	**1484 (57·6)**	**215 (49·9)**	**1699 (56·5)**	**290 (40·3)**	**34 (28·8)**	**324 (38·7)**
Malaise/Fatigue	**1186 (36·0)**	**163 (29·7)**	**1349 (35·1)**	**1036 (40·2)**	**142 (32·9)**	**1178 (39·2)**	**150 (20·8)**	**21 (17·8)**	**171 (20·4)**
Grade 1	961 (29·2)	134 (24·4)	1095 (28·5)	831 (32·3)	117 (27·1)	948 (31·5)	130 (18·1)	17 (14·4)	147 (17·5)

	All, n (%)			≥ 20 to < 65 years, n (%)			≥ 65 years, n (%)		
	MVC-COV1901 (N = 3295)	**Placebo (N = 549)**	**Total (N = 3844)**	**MVC-COV1901 (N = 2575)**	**Placebo (N = 431)**	**Total (N = 3006)**	**MVC-COV1901 (N = 720)**	**Placebo (N = 118)**	**Total (N = 838)**
Grade 2	203 (6·2)	27 (4·9)	230 (6·0)	185 (7·2)	23 (5·3)	208 (6·9)	18 (2·5)	4 (3·4)	22 (2·6)
Grade 3	22 (0·7)	2 (0·4)	24 (0·6)	20 (0·8)	2 (0·5)	22 (0·7)	2 (0·3)	0	2 (0·2)
Myalgia	**908 (27·6)**	**91 (16·6)**	**999 (26·0)**	**757 (29·4)**	**79 (18·3)**	**836 (27·8)**	**151 (21·0)**	**12 (10·2)**	**163 (19·5)**
Grade 1	764 (23·2)	83 (15·1)	847 (22·0)	629 (24·4)	73 (16·9)	702 (23·4)	135 (18·8)	10 (8·5)	145 (17·3)
Grade 2	126 (3·8)	5 (0·9)	131 (3·4)	112 (4·3)	4 (0·9)	116 (3·9)	14 (1·9)	1 (0·8)	15 (1·8)
Grade 3	18 (0·5)	3 (0·5)	21 (0·5)	16 (0·6)	2 (0·5)	18 (0·6)	2 (0·3)	1 (0·8)	3 (0·4)
Headache	**730 (22·2)**	**110 (20·0)**	**840 (21·9)**	**631 (24·5)**	**94 (21·8)**	**725 (24·1)**	**99 (13·8)**	**16 (13·6)**	**115 (13·7)**
Grade 1	630 (19·1)	95 (17·3)	725 (18·9)	537 (20·9)	81 (18·8)	618 (20·6)	93 (12·9)	14 (11·9)	107 (12·8)
Grade 2	93 (2·8)	15 (2·7)	108 (2·8)	87 (3·4)	13 (3·0)	100 (3·3)	6 (0·8)	2 (1·7)	8 (1·0)
Grade 3	7 (0·2)	0	7 (0·2)	7 (0·3)	0	7 (0·2)	0	0	0
Diarrhoea	**497 (15·1)**	**69 (12·6)**	**566 (14·7)**	**422 (16·4)**	**63 (14·6)**	**485 (16·1)**	**75 (10·4)**	**6 (5·1)**	**81 (9·7)**
Grade 1	411 (12·5)	56 (10·2)	467 (12·1)	350 (13·6)	52 (12·1)	402 (13·4)	61 (8·5)	4 (3·4)	65 (7·8)
Grade 2	75 (2·3)	11 (2·0)	86 (2·2)	62 (2·4)	9 (2·1)	71 (2·4)	13 (1·8)	2 (1·7)	15 (1·8)
Grade 3	11 (0·3)	2 (0·4)	13 (0·3)	10 (0·4)	2 (0·5)	12 (0·4)	1 (0·1)	0	1 (0·1)
Nausea/Vomiting	**254 (7·7)**	**37 (6·7)**	**291 (7·6)**	**219 (8·5)**	**33 (7·7)**	**252 (8·4)**	**35 (4·9)**	**4 (3·4)**	**39 (4·7)**
Grade 1	226 (6·9)	33 (6·0)	259 (6·7)	192 (7·5)	29 (6·7)	221 (7·4)	34 (4·7)	4 (3·4)	38 (4·5)
Grade 2	26 (0·8)	3 (0·5)	29 (0·8)	25 (1·0)	3 (0·7)	28 (0·9)	1 (0·1)	0	1 (0·1)

	All, n (%)			≥ 20 to < 65 years, n (%)			≥ 65 years, n (%)		
	MVC-COV1901 (N = 3295)	**Placebo (N = 549)**	**Total (N = 3844)**	**MVC-COV1901 (N = 2575)**	**Placebo (N = 431)**	**Total (N = 3006)**	**MVC-COV1901 (N = 720)**	**Placebo (N = 118)**	**Total (N = 838)**
Grade 3	2 (0·1)	1 (0·2)	3 (0·1)	2 (0·1)	1 (0·2)	3 (0·1)	0	0	0
Fever	**23 (0·7)**	**2 (0·4)**	**25 (0·7)**	**16 (0·6)**	**2 (0·5)**	**18 (0·6)**	**7 (1·0)**	**0**	**7 (0·8)**
Grade 1	14 (0·4)	2 (0·4)	16 (0·4)	8 (0·3)	2 (0·5)	10 (0·3)	6 (0·8)	0	6 (0·7)
Grade 2	6 (0·2)	0	6 (0·2)	6 (0·2)	0	6 (0·2)	0	0	0
Grade 3	2 (0·1)	0	2 (0·1)	2 (0·1)	0	2 (0·1)	0	0	0
Grade 4	1 (<0·1)	0	1 (<0·1)	0	0	0	1 (<0·1)	0	1 (<0·1)

Table S6. Summary of Unsolicited Adverse Events and Other Adverse Events

	All, n (%)			≥ 20 to < 65 years, n (%)			≥ 65 years, n (%)		
	MVC-COV1901 (N = 3295)	Placebo (N = 549)	Total (N =3844)	MVC-COV1901 (N = 2575)	Placebo (N = 431)	Total (N = 3006)	MVC-COV1901 (N = 720)	Placebo (N = 118)	Total (N = 838)
Unsolicited AEs	932 (28·3)	149 (27·1)	1081 (28·1)	767 (29·8)	123 (28·5)	890 (29·6)	165 (22·9)	26 (22·0)	191 (22·8)
Related unsolicited AEs	406 (12·3)	62 (11·3)	468 (12·2)	340 (13·2)	56 (13·0)	396 (13·2)	66 (9·2)	6 (5·1)	72 (8·6)
Unsolicited AEs ≥ Grade 3	93 (2·8)	11 (2·0)	104 (2·7)	86 (3·3)	10 (2·3)	96 (3·2)	7 (1·0)	1 (0·8)	8 (1·0)
Related unsolicited AEs ≥ Grade 3	21 (0·6)	4 (0·7)	25 (0·7)	20 (0·8)	4 (0·9)	24 (0·8)	1 (0·1)	0	1 (0·1)
SAEs	18 (0·5)	1 (0·2)	19 (0·5)	16 (0·6)	1 (0·2)	17 (0·6)	2 (0·3)	0	2 (0·2)
Related SAEs	0	0	0	0	0	0	0	0	0
AESI	1 (<0·1)	0	1 (<0·1)	0	0	0	1 (0·1)	0	1 (0·1)
VAED	0	0	0	0	0	0	0	0	0
AEs leading to study intervention discontinuation	2 (0·1)	1 (0·2)	3 (0·1)	0	1 (0·2)	1 (<0·1)	2 (0·3)	0	2 (0·2)
AEs leading to study withdrawal	1 (<0·1)	0	1 (<0·1)	0	0	0	1 (0·1)	0	1 (0·1)
Death	0	0	0	0	0	0	0	0	0

Abbreviations: AE = adverse event; AESI = adverse events of special interest; CI = confidence interval; N = number of participants in the population; n = number of participants with events; SAE = serious adverse event; VAED = vaccine-associated enhanced disease

Table S7. Wild Type SARS-CoV-2 Neutralizing Antibody Geometric Mean Titres (PPI Subset)

Visit	Statistics	MVC-COV1901	Placebo	Ratio (MVC-COV1901 / Placebo)	*P*-value [1]
All Participants of PPI Subset, N		**903**	**150**		
Day 1 (Vaccination 1)	n	903	150		
	GMT	4·06	4·02	1·01	0·2406
	95% CI of GMT	(4·02, 4·09)	(3·98, 4·07)	(0·99, 1·02)	
Day 57	n	903	150		
	GMT	662·31	4·00	165·58	<0·0001
	95% CI of GMT	(628·66, 697·75)	(4·00, 4·00)	(157·16, 174·44)	
	n	903	150		
	GMT ratio	163·22	0·99	164·15	<0·0001
	95% CI of GMT ratio	(155·01, 171·87)	(0·98, 1·01)	(155·71, 173·05)	
Subgroup: 20 to 64 years of age, N		**682**	**113**		
Day 1 (Vaccination 1)	n	682	113		
	GMT	4·06	4·03	1·01	0·4119
	95% CI of GMT	(4·02, 4·11)	(3·97, 4·09)	(0·99, 1·03)	
Day 57	n	682	113		
	GMT	732·89	4·00	183·22	<0·0001
	95% CI of GMT	(692·41, 775·74)	(4·00, 4·00)	(173·10, 193·94)	
	n	682	113		
	GMT ratio	180·45	0·99	181·82	<0·0001

Visit	Statistics	MVC-COV1901	Placebo	Ratio (MVC-COV1901 / Placebo)	*P*-value [1]
	95% CI of GMT ratio	(170·59, 190·89)	(0·98, 1·01)	(171·55, 192·70)	
Subgroup: ≥ 65 years of age, N		**221**	**37**		
Day 1 (Vaccination 1)	n	221	37		
	GMT	4·05	4·00	1·01	0·1730
	95% CI of GMT	(3·98, 4·11)	(4·00, 4·00)	(0·99, 1·03)	
Day 57	n	221	37		
	GMT	484·54	4·00	121·14	<0·0001
	95% CI of GMT	(433·16, 542·01)	(4·00, 4·00)	(108·29, 135·50)	
	n	221	37		
	GMT ratio	119·75	1·00	119·75	<0·0001
	95% CI of GMT ratio	(107·16, 133·82)	(1·00, 1·00)	(107·16, 133·82)	

Abbreviations: N = number of participants in the population; n = number of participants with available data; GMT = geometric mean titre; CI = confidence interval

Note: Blood samples on Day 1 for immunogenicity test were collected before the administration of study intervention. GMT ratio was compared to Day 1 (prior to first dose).

[1] *P*-value based on two-sample t test or Wilcoxon rank sum test.

Table S8. Seroconversion Rate Based on the Wild Type SARS-CoV-2 Neutralizing Antibody Titres at Day 57 (PPI Subset)

Visit	Statistics	MVC-COV1901	Placebo	Treatment Difference % [1] (MVC-COV1901 minus Placebo)	*P*-value [2]
All Participants of PPI Subset, N		**903**	**150**		
Day 57	n	903	150		
	Seroconversion, n (%)	901 (99·8)	0	99·8	<0·0001
	95% CI	(99·20, 99·97)	(0·00, 2·43)	(97·51, 99·98)	
Subgroup: 20 to 64 years of age, N4		**682**	**113**		
Day 57	n	682	113		
	Seroconversion, n (%)	681 (99·9)	0	99·9	<0·0001
	95% CI	(99·19, 100·00)	(0·00, 3·21)	(96·79, 100·00)	
Subgroup: ≥ 65 years of age, N		**221**	**37**		
Day 57	n	221	37		
	Seroconversion, n (%)	220 (99·5)	0	99·5	<0·0001
	95% CI	(97·50, 99·99)	(0·00, 9·49)	(90·46, 99·99)	

Abbreviations: N = number of participants in the population; n = number of participants in the specific category; %=percentage of participants with available data (n) as the denominator; CI = confidence interval.

Note: Seroconversion was defined as at least 4-fold increase of post-study intervention antibody titres from the baseline titre or from half of the lower limit of detection if undetectable at baseline. Blood samples on Day 1 for immunogenicity test were collected before the administration of study intervention.

[1] Treatment Difference was presented with the asymptotic 95% CI. In the case of small cell count (expected count less than 5), exact 95% CI was applied alternatively.

[2] *P*-value: Pearson's Chi-square test. In the case of small cell count (expected count less than 5), Fisher's exact test was applied alternatively.

Table S9. Anti-Spike IgG Geometric Mean Titres (PPI Subset)

Visit	Statistics	MVC-COV1901	Placebo	Ratio (MVC/Placebo)	*P*-value [1]
All Participants of PPI Subset, N		**903**	**150**		
Day 1 (Vaccination 1)	n	903	150		
	GMT	52·71	54·16	0·97	0·3870
	95% CI of GMT	(51·65, 53·79)	(51·09, 57·40)	(0·92, 1·04)	
Day 29 (Vaccination 2)	n	901	147		
	GMT	430·48	55·68	7·73	<0·0001
	95% CI of GMT	(398·68, 464·83)	(51·71, 59·95)	(6·95, 8·60)	
	n	901	147		
	GMT ratio	8·17	1·03	7·96	<0·0001
	95% CI of GMT ratio	(7·56, 8·82)	(0·96, 1·10)	(7·18, 8·82)	
Day 43	n	898	149		
	GMT	8262·17	57·64	143·34	<0·0001
	95% CI of GMT	(7801·94, 8749·54)	(52·10, 63·76)	(127·65, 160·96)	
	n	898	149		
	GMT ratio	156·70	1·06	147·31	<0·0001
	95% CI of GMT ratio	(147·52, 166·46)	(0·96, 1·17)	(131·31, 165·26)	
Day 57	n	903	150		
	GMT	5745·35	54·43	105·56	<0·0001
	95% CI of GMT	(5464·49, 6040·64)	(51·66, 57·34)	(98·21, 113·46)	
	n	903	150		

Visit	Statistics	MVC-COV1901	Placebo	Ratio (MVC/Placebo)	*P*-value [1]
	GMT ratio	109·00	1·01	108·46	<0·0001
	95% CI of GMT ratio	(103·32, 115·00)	(0·96, 1·05)	(101·07, 116·38)	
Subgroup: 20 to 64 years of age, N		**682**	**113**		
Day 1 (Vaccination 1)	n	682	113		
	GMT	53·16	53·97	0·98	0·6524
	95% CI of GMT	(51·87, 54·49)	(50·59, 57·58)	(0·92, 1·05)	
Day 29 (Vaccination 2)	n	682	112		
	GMT	524·24	55·98	9·36	<0·0001
	95% CI of GMT	(482·66, 569·41)	(51·10, 61·33)	(8·28, 10·59)	
	n	682	112		
	GMT ratio	9·86	1·04	9·51	<0·0001
	95% CI of GMT ratio	(9·06, 10·73)	(0·95, 1·13)	(8·42, 10·75)	
Day 43	n	679	113		
	GMT	9637·58	59·39	162·28	<0·0001
	95% CI of GMT	(9070·69, 10239·89)	(52·16, 67·61)	(138·63, 189·97)	
	n	679	113		
	GMT ratio	181·24	1·10	164·71	<0·0001
	95% CI of GMT ratio	(169·83, 193·42)	(0·97, 1·25)	(142·79, 189·99)	
Day 57	n	682	113		
	GMT	6520·95	54·79	119·02	<0·0001
	95% CI of GMT	(6188·26, 6871·32)	(51·47, 58·32)	(109·74, 129·10)	

Visit	Statistics	MVC-COV1901	Placebo	Ratio (MVC/Placebo)	*P*-value [1]
	n	682	113		
	GMT ratio	122·66	1·02	120·84	<0·0001
	95% CI of GMT ratio	(115·85, 129·88)	(0·96, 1·07)	(111·65, 130·79)	
Subgroup: ≥ 65 years of age, N		**221**	**37**		
Day 1 (Vaccination 1)	n	221	37		
	GMT	51·34	54·72	0·94	0·3584
	95% CI of GMT	(49·67, 53·06)	(47·81, 62·64)	(0·82, 1·08)	
Day 29 (Vaccination 2)	n	219	35		
	GMT	233·05	54·70	4·26	<0·0001
	95% CI of GMT	(198·91, 273·05)	(48·89, 61·20)	(3·51, 5·16)	
	n	219	35		
	GMT ratio	4·54	0·99	4·56	<0·0001
	95% CI of GMT ratio	(3·88, 5·31)	(0·94, 1·05)	(3·86, 5·40)	
Day 43	n	219	36		
	GMT	5125·71	52·48	97·68	<0·0001
	95% CI of GMT	(4538·27, 5789·19)	(47·57, 57·89)	(83·67, 114·03)	
	n	219	36		
	GMT ratio	99·81	0·96	104·35	<0·0001
	95% CI of GMT ratio	(87·87, 113·38)	(0·89, 1·02)	(90·42, 120·42)	
Day 57	n	221	37		
	GMT	3887·09	53·35	72·86	<0·0001

Visit	Statistics	MVC-COV1901	Placebo	Ratio (MVC/Placebo)	*P*-value [1]
	95% CI of GMT	(3476·08, 4346·71)	(48·46, 58·72)	(62·97, 84·31)	
	n	221	37		
	GMT ratio	75·71	0·97	77·67	<0·0001
	95% CI of GMT ratio	(67·28, 85·20)	(0·90, 1·06)	(67·24, 89·71)	

Abbreviations: N = number of participants in the population; n = number of participants with available data; GMT = geometric mean titre; CI = confidence interval

Note: Blood samples or immunogenicity test were collected before the administration of study intervention· GMT ratio was compared to Day 1 (prior to first dose).

[1] *P*-value based on two-sample t test or Wilcoxon rank sum test.

Table S10. Illustration of Day 57 neutralising antibody GMTs and the converted WHO IU/mL & BAU/mL

	Neutralising Antibody GMT	International Unit (IU/mL)	Binding Antibody Unit (BAU/mL)
All Participant (N = 903)	662·3	408	524
20-64 years age group (N = 682)	732·9	454	595
≥ 65 years age group (N = 221)	484·5	296	355

Table S11. Seroconversion Rate Based on the anti-Spike IgG antibody titres on Day 57 (PPI Subset)

Visit	Statistics	MVC-COV1901	Placebo	Treatment Difference % [1] (MVC-COV1901 minus Placebo)	*P*-value [2]
All Participants of PPI Subset, N		**903**	**150**		
Day 29 (Vaccination 2)	n	901	147		
	Seroconversion, n (%)	670 (74·4)	2 (1·4)	73·0	<0·0001
	95% CI	(71·38, 77·18)	(0·17, 4·83)	(68·83, 76·22)	
Day 43	n	898	149		
	Seroconversion, n (%)	895 (99·7)	2 (1·3)	98·3	<0·0001
	95% CI	(99·03, 99·93)	(0·16, 4·76)	(95·11, 99·58)	
Day 57	n	903	150		
	Seroconversion, n (%)	899 (99·6)	0	99·6	<0·0001
	95% CI	(98·87, 99·88)	(0·00, 2·43)	(97·37, 99·89)	
Subgroup: 20 to 64 years of age, N		**682**	**113**		
Day 29 (Vaccination 2)	n	682	112		
	Seroconversion, n (%)	552 (80·9)	2 (1·8)	79·2	<0·0001
	95% CI	(77·79, 83·82)	(0·22, 6·30)	(74·09, 82·70)	
Day 43	n	679	113		
	Seroconversion, n (%)	677 (99·7)	2 (1·8)	97·9	<0·0001
	95% CI	(98·94, 99·96)	(0·22, 6·25)	(93·68, 99·48)	
Day 57	n	682	113		

Visit	Statistics	MVC-COV1901	Placebo	Treatment Difference % [1] (MVC-COV1901 minus Placebo)	*P*-value [2]
	Seroconversion, n (%)	679 (99·6)	0	99·6	<0·0001
	95% CI	(98·72, 99·91)	(0·00, 3·21)	(96·63, 99·91)	
Subgroup: ≥ 65 years of age, N		**221**	**37**		
Day 29 (Vaccination 2)	n	219	37		
	Seroconversion, n (%)	118 (53·9)	0	53·9	<0·0001
	95% CI	(47·04, 60·62)	(0·00, 10·00)	(42·11, 60·82)	
Day 43	n	219	36		
	Seroconversion, n (%)	218 (99·5)	0	99·5	<0·0001
	95% CI	(97·48, 99·99)	(0·00, 974)	(90·21, 99·99)	
Day 57	n	221	37		
	Seroconversion, n (%)	220 (99·5)	0	99·5	<0·0001
	95% CI	(97·50, 99·99)	(0·00, 9·49)	(90·46, 99·99)	

Abbreviations: N = number of participants in the population; n = number of participants in the specific category; %=percentage of participants with available data (n) as the denominator; CI = confidence interval.

Note: Seroconversion was defined as at least 4-fold increase of post-study intervention antibody titres from the baseline titre or from half of the lower limit of detection if undetectable at baseline. Blood samples for immunogenicity test were collected before the administration of study intervention.

[1] Treatment Difference was presented with the asymptotic 95% CI. In the case of small cell count (expected count less than 5), exact 95% CI was applied alternatively.

[2] *P*-value: Pearson's Chi-square test. In the case of small cell count (expected count less than 5), Fisher's exact test was applied alternatively.

Title Page

Clinical Study Protocol

A Phase II, Prospective, Double-blinded, Multi-Center, Multi-Regional Study to Evaluate the Safety, Tolerability, and Immunogenicity of the SARS-CoV-2 Vaccine Candidate MVC-COV1901

Protocol Number:	CT-COV-21
Amendment Number:	3
Test Product:	MVC-COV1901
Control Product:	Placebo
Study Phase:	II
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):	Not applicable
Protocol Version and Date:	Version 3.0 , 02-JUN-2021
Brief Title:	A Phase II study to evaluate safety, tolerability, and immunogenicity of MVC-COV1901 vaccine against SARS-CoV-2 in participants aged 20 and above

Document History

Document	Protocol version	Date
Amendment 3	*version 3.0*	*02-JUN-2021*
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Amendment 1	*version 2.0*	*29-DEC-2020*
Original Protocol	*version 1.0*	*27-NOV-2020*

PROTOCOL APPROVAL SIGNATURE PAGE

Protocol Title:	A Phase II, Prospective, Double-blinded, Multi-Center, Multi-Regional Study to Evaluate the Safety, Tolerability, and Immunogenicity of the SARS-CoV-2 Vaccine Candidate MVC-COV1901
Protocol Number:	CT-COV-21

I have read and understand the contents of this clinical protocol for Study No. **CT-COV-21**, **Version 3.0**, dated **02-JUN-2021** 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 Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for current Good Clinical Practice (GCP) and applicable regulatory requirements.

Sponsor Signatory

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Medical Affairs Associate Director

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Signature

Date

STATEMENT OF COMPLIANCE

Protocol Title:	A Phase II, Prospective, Double-blinded, Multi-Center, Multi-Regional Study to Evaluate the Safety, Tolerability, and Immunogenicity of the SARS-CoV-2 Vaccine Candidate MVC-COV1901
Protocol Number:	CT-COV-21
Protocol Version and Date	Version 3.0, 02-JUN-2021

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

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1. Protocol Summary

1.1. Synopsis

Protocol Title:

A Phase II, Prospective, Double-blinded, Multi-Center, Multi-Regional Study to Evaluate the Safety, Tolerability, and Immunogenicity of the SARS-CoV-2 Vaccine Candidate MVC-COV1901

Brief Title:

A Phase II study to evaluate safety, tolerability, and immunogenicity of MVC-COV1901 vaccine against SARS-CoV-2 in participants aged 20 and above

Rationale:

A new virus, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has caused a worldwide outbreak of a pneumonia-like respiratory disease named coronavirus disease 2019 (COVID-19) since December 2019. As of early November 2020, more than 49 million confirmed cases and over 1 million deaths due to COVID-19 have been reported globally. There is currently no cure for the potentially lethal COVID-19. The availability of a vaccine is considered a promising approach to augment anti-SARS-CoV-2 immunity. There is yet to be a vaccine approved to prevent infection by SARS-CoV-2 or COVID-19.

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. MVC-COV1901 also contains cytosine phosphoguanine (CpG) 1018 and aluminum hydroxide ($Al[OH]_3$) as adjuvants which enhance recognition by the innate immune system. The current study is aimed to evaluate the safety, tolerability, and immunogenicity of the subunit vaccine MVC-COV1901 against SARS-CoV-2 in adult participants. Due to the highly contagious nature of SARS-CoV-2, partly due to transmission via asymptomatic infected individuals, the prompt development of a safe and effective vaccine is of utmost importance for regional and global public health.

Objectives and Endpoints:

Objectives	Endpoints
Primary Safety	
To evaluate the safety and tolerability of MVC-COV1901 from Visit 2 (Day 1) to Visit 7 (28 days after the second dose of study intervention)	For all participants who receive at least one dose of study intervention, the safety and tolerability of MVC-COV1901 from Visit 2 (Day 1) to Visit 7 (28 days after the second dose of study intervention) in terms of 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) • Solicited systemic AEs (up to 7 days after each dose of study intervention) • Unsolicited AEs (up to 28 days after each dose of study intervention) • AE of special interest (AESI) • Vaccine-associated enhanced disease (VAED) • Serious adverse events (SAEs) Note: - Solicited local AEs: pain/tenderness, erythema/redness, induration/swelling - Solicited systemic AEs: fever, malaise/fatigue, myalgia, headache, nausea/vomiting, diarrhea
Primary Immunogenicity	
To evaluate the immunogenicity of MVC-COV1901, as compared to placebo, in terms of neutralizing antibody titers	For participants in the Immunogenicity Subset, the neutralizing antibody titers at Visit 7 (28 days after the second dose of study intervention) in terms of: • Geometric mean titers (GMT) • Seroconversion rate (SCR) • GMT ratio 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 - 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 over the study period	For all participants who receive at least one dose of study intervention, the safety of MVC-COV1901 within the whole study period in terms of the number and percentage of participants with the occurrence of: • ≥ Grade 3 AE • AESI • VAED • SAE
Secondary Immunogenicity	
To evaluate the lot-to-lot consistency of MVC-COV1901 in participants of the ≥ 20 to < 65 years age group	For participants in the ≥ 20 to < 65 years age group in the Immunogenicity Subset, the equivalence of the neutralizing antibody GMTs among 3 different lots of MVC-COV1901 at Visit 7 (28 days after second dose of study intervention)
To evaluate the immunogenicity of MVC-COV1901, as compared to placebo, in terms of antigen-specific immunoglobulin titers and neutralizing antibody titers	For all participants in the Immunogenicity Subset, the antigen-specific immunoglobulin titers and neutralizing antibody titers at Visit 4 (28 days after the first dose of study intervention), Visit 6 (14 days after the second dose of study intervention), Visit 7 (28 days after the second dose of study intervention) and Visit 9 (180 days after the second dose of study intervention) in terms of: • GMT • SCR • GMT ratio
Exploratory	
To estimate the efficacy of MVC-COV1901, as compared to placebo, in the prevention of COVID-19	For all participants who receive at least one dose of study intervention, • The number of laboratory-confirmed COVID-19 cases occurring ≥ 15 days after any dose of study intervention. • The number of laboratory-confirmed COVID-19 severe cases occurring ≥ 15 days after any dose of study intervention.

Overall Design:

This is a Phase II, prospective, placebo-controlled, double-blinded (investigator/site staff and participants), multi-center, multi-regional study; the Sponsor will be blinded until the interim analysis. Participants who are generally healthy or with stable pre-existing health conditions will be randomized, stratified by age (≥ 20 to < 65 years and ≥ 65 years of age). All eligible participants will be randomized to receive either MVC-COV1901 or placebo in a 6:1 ratio. Participants of ≥ 20 to < 65 years of age in the Immunogenicity Subset will be randomized to 1 of 3 lots of MVC-COV1901 or placebo in a 2:2:2:1 ratio (Lot 1:Lot 2:Lot 3:placebo).

The study consists of 6 on-site visits and 3 phone calls:

- Day -28 to Day -1, Visit 1 (Screening)
- Day 1, Visit 2 (First dose of study intervention)
- Day 8 ± 2, Visit 3 (Phone call)
- Day 29 ± 3, Visit 4 (Second dose of study intervention)
- Day 36 ± 2, Visit 5 (Phone call)
- Day 43 ± 3, Visit 6
- Day 57 ± 3, Visit 7
- Day 85 ± 3, Visit 8 (Phone call)
- Day 209 ± 14, Visit 9

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

An Independent Data Monitoring Committee (IDMC) will review the accumulated safety data at the pre-specified timepoints and will review the cumulative SAEs monthly. An interim analysis of safety, immunogenicity, and lot-to-lot consistency will be carried out under the condition of 1 month after all participants have completed the second dose of study intervention *and* 2 months after half of the participants have completed the second dose of study intervention.

Brief Summary:

The purpose of this study is to assess the safety and immunogenicity of MVC-COV1901 vaccine compared to placebo in participants who are generally healthy or with stable pre-existing health conditions. Study details include:

- The study duration per participant will be approximately 237 days (28 days screening, 29 days treatment, 180 days follow-up).
- The treatment duration will be approximately 29 days.
- The visit frequency will be 6 on-site visits and 3 phone calls.

Number of Participants:

A total of approximately 3700 participants will be randomly assigned to study intervention. In the stratification by age, a minimum of approximately 20% of the participants will be ≥ 65 years of age. Among them, 1090 randomized participants (820 participants in the ≥ 20 to < 65 years age group and 270 in the ≥ 65 years age group) will be included in the Immunogenicity Subset for immunogenicity assessments.

Study Population:

- **Inclusion Criteria**

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

1. Male or female participant ≥ 20 to < 65 years, or ≥ 65 years of age at randomization.
2. Healthy adults or adults with pre-existing medical conditions who are in stable condition. 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 participant must:
    a. Be either 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. Or, if of childbearing potential, be abstinent or agree to use medically effective contraception from 14 days before screening to 30 days following the last injection of study intervention. Acceptable forms include:
        i. Implanted hormonal methods of contraception or placement of an intrauterine device or intrauterine 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
    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 has not travelled overseas within 14 days of screening and will not have any oversea travelling throughout the study period.
6. 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 in 30 days after last administration of study intervention.
2. Employees at the investigator's site, of the Sponsor or the contract research organization (CRO) directly involved in the conduct of the study.

<u>Prior/Concomitant Therapy</u>

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.

Medical Conditions

9. Immunosuppressive illness or immunodeficient state, including hematologic malignancy, history of solid organ, bone marrow transplantation, or asplenia.
10. A history of autoimmune disease (systemic lupus, rheumatoid arthritis, scleroderma, polyarthritis, thyroiditis, Guillain-Barré syndrome, etc.).
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 injection or phlebotomy.
13. Human immunodeficiency virus (HIV) antibody positive participants with CD4 count < 350 cells/mm^3 or a detectable HIV viral load within the past year (low level variations from 50-500 viral copies/mL or equivalent which do not lead to changes in antiretroviral therapy [ART] are permitted).
14. Hepatitis B surface antigen (HBsAg) positive participant with positive hepatitis B e antigen (HBeAg) or abnormal liver function.
15. Hepatitis C virus (HCV) antibody positive participants with detectable HCV ribonucleic acid (RNA) viremia in recent 12 weeks.
16. Participant with ongoing acute diseases or serious medical conditions which will interfere with adherence to study requirements, or the evaluation of any study endpoint.
    Acute diseases or serious medical conditions include cardiovascular (e.g. New York Heart Association Grade III or IV), pulmonary (e.g. chronic obstructive pulmonary disease stage III or IV), hepatic (e.g. Child-Pugh Class C), neurologic (e.g. dementia), metabolic (e.g. diabetes mellitus with hemoglobin A1c [HbA1c] > 8%), renal (Stage 3 or worse chronic kidney disease), psychiatric condition (e.g. alcoholism, drug abuse), current severe infections, medical history, physical findings, or laboratory abnormality that in the investigators' opinion are not in stable condition and participating in the study could adversely affect the safety of the participant.
17. Participant with previous known or potential exposure to SARS-CoV-1 or 2 viruses (EXCEPT for those who have been tested negative and completed the 14-day self-managements/ home quarantines/ home isolations) or received any other COVID-19 vaccine.
18. Participant with 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.
19. Body (oral, rectal, or ear) temperature $\geq 38.0°C$ 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:

All participants will be randomized to one of the following 2 treatment arms:

- Vaccine (MVC-COV1901): approximately 3180 participants will receive 2 doses of MVC-COV1901 at 15 mcg of S-2P protein at Visit 2 (Day 1) and Visit 4 (Day 29) via intramuscular (IM) injection in the deltoid region
- Placebo: approximately 530 participants will receive 2 doses of placebo containing only saline at Visit 2 (Day 1) and Visit 4 (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:

All measured variables and derived parameters will be listed by participant and tabulated by descriptive statistics. Summary descriptive statistics will be provided for all safety, immunogenicity, exploratory efficacy, and baseline/demographic 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% confidence interval (CI) of mean and median (when appropriate). Categorical variables will be summarized with number and percentage of participants. Significance tests (2-tailed, alpha = 0.05) without alpha adjustment will be performed for pairwise comparison where appropriate and *P*-value will be rounded to four decimal places, if applicable.

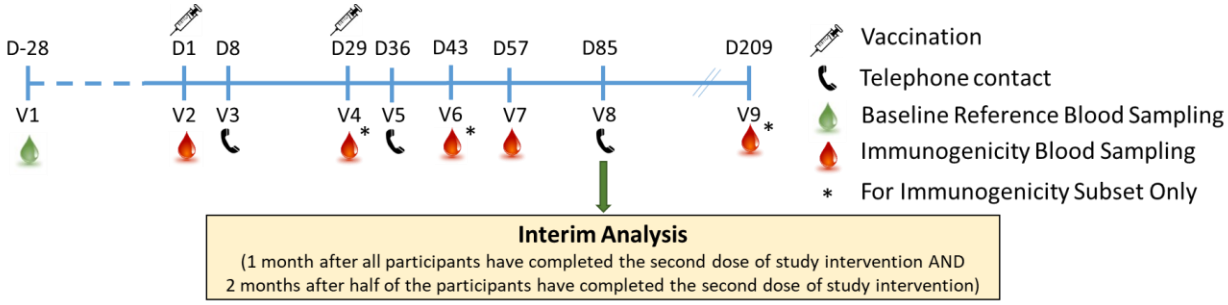
Lot-to-lot consistency will be analyzed in the ≥ 20 to < 65 years group of the Immunogenicity Subset only. Equivalence among the 3 lots will be demonstrated if for each pair of lots, the two-sided 95% CIs of the GMT ratio is entirely within 0.5 and 2.0.

The total sample size, the sample size of each age subgroup, and of each treatment arm are based on the minimum requirement for a Phase II vaccine study as agreed with the Taiwan FDA. For calculating the sample size of lot-to-lot consistency, the statistical methodology is based on the use of a two-sided 95% CI [100(1-2α)%], calculated using the differences of the post-vaccination GMT of neutralizing antibody between pairs of lots.

Data Monitoring Committee: Yes

An IDMC will be appointed for this study and the details of the committee will be provided in the IDMC charter. The IDMC is a group of independent experts who are appointed to monitor the safety of the study. The composition of the committee is dependent upon the scientific or medical skills and knowledge required for monitoring the study.

1.2. Schema


D-28
D1
D8
D29
D36
D43
D57
D85
D209
V1
V2
V3
V4
V5
V6
V7
V8
V9
Vaccination
Telephone contact
Baseline Reference Blood Sampling
Immunogenicity Blood Sampling
For Immunogenicity Subset Only
Interim Analysis
(1 month after all participants have completed the second dose of study intervention AND
2 months after half of the participants have completed the second dose of study intervention)

1.3. Schedule of Activities (SoA)

Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**ET[14]**	Unscheduled[15]
Visit Day	-28 to -1	1	8 (±2)	29 (±3)	36 (7±2 days after V4)	43 (14±3 days after V4)	57 (28±3 days after V4)	85 (56±3 days after	209 (180±14 days after V4)	Early Termination Visit	NA
Visit Type	Screening	Vaccination 1	Phone Call	Vaccination 2	Phone Call	Immunogenicity Visit	Immunogenicity Visit	Phone Call	EOS	ET	NA
Procedures											
Informed consent	X										
Medical history	X	X									
Demographics	X										
Concomitant medication	X	X	X	X	X	X	X	X	X	X	
Inclusion/Exclusion criteria	X	X									
Urine pregnancy test[1]	X	X		X		X	X			X[14a]	Per investigator's discretion
Body height and weight	X										
Physical examination[2]	X[2a]	X[2b]		X[2b]		X[2b]	X[2b]		X[2b]	X[2b]	
Serology test[3]	X										
Hematology, biochemistry, and immunology test[4]	X										
ECG[5]	X										
Vital signs[6]	X	X		X							
Randomization		X									
Elimination criteria[7]		X	X	X	X	X	X	X	X	X	
Contraindication to study intervention[8]		X		X							

Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**ET[14]**	Unscheduled[15]
Visit Day	-28 to -1	1	8 (±2)	29 (±3)	36 (7±2 days after V4)	43 (14±3 days after V4)	57 (28±3 days after V4)	85 (56±3 days after	209 (180±14 days after V4)	Early Termination Visit	NA
Visit Type	Screening	Vaccination 1	Phone Call	Vaccination 2	Phone Call	Immunogenicity Visit	Immunogenicity Visit	Phone Call	EOS	ET	NA
Procedures											
Blood sampling for immunogenicity[9]		X[9a]		X[9b]		X[9b]	X[9a]		X[9b]	X[14b]	
Administration of study intervention[10]		X		X							
Distribution of diary cards		X		X							
Diary cards review and return				X		X	X				
Solicited symptoms[11]		X	X	X	X					X[14c]	Per investigator's discretion
Unsolicited symptoms[12]		X	X	X	X	X	X			X[14d]	
≥ Grade 3 AE, AESI, VAED, SAE			X								
Laboratory-confirmed SARS-CoV-2 infection or COVID-19 cases[13]			X								
Study completion									X		

Abbreviation: AE = adverse events; AESI = adverse events of special interest; ALT = alanine transferase; ANA = antinuclear antibody; ANCA = anti-neutrophil cytoplasmic antibodies; APTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; c-ANCA = cytoplasmic anti-neutrophil cytoplasmic antibodies; COVID-19 = coronavirus disease 2019; Cr = creatinine; dsDNA = double stranded deoxyribonucleic acid; ECG= Electrocardiography; EOS = end of study; ET = early termination; Hb = hemoglobin; HBsAg = hepatitis B surface antigen; HBeAg = hepatitis B e antigen; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; Hct = hematocrit; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; NA = not applicable; p-ANCA = perinuclear anti-neutrophil cytoplasmic antibodies; 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. Urine pregnancy test (beta-hCG): for female participants with childbearing potential only.
2. Physical examination: (2a) 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; (2b) targeted examination will be performed if indicated by any change in the participant's health condition since the previous visit as determined by investigator.
3. Serology includes HIV antibody or rapid test, HBsAg, HBeAg, HCV antibody.
4. Hematology: Hb, RBC, Hct, MCV, MCH, MCHC, reticulocyte, WBC, differential of leukocytes, platelets, prothrombin time, and APTT
   Biochemistry: HbA1c, BUN, Cr, ALT, AST, sodium, potassium and chloride
   Immunology: ANA, anti-dsDNA antibody, ANCA (including c-ANCA and p-ANCA).
   Hematology, biochemistry and immunology tests at screening are to provide a reference point for evaluation of AEs during the study, if needed.
5. Baseline ECG can be performed at Visit 1 or Visit 2 before the subject receives the first vaccination. The baseline ECG is to provide a reference point for evaluation of AEs during the study, if needed.
6. Vital Signs: body temperature, pulse rate, respiratory rate, and blood pressure at sitting position. Vital signs will be performed before administration of study intervention and approximately 30 minutes after administration of study intervention at Visit 2 and Visit 4.
7. Elimination 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 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.
8. 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 (not including any coronavirus vaccine other than study intervention , which is prohibited; participant may be rescheduled); any non-live-attenuated vaccine within 7 days before each administration of study intervention (not including any coronavirus vaccine other than study intervention, which is prohibited; 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.
9. Blood sampling for immunogenicity: (9a) blood samples will be collected for all randomized participants; (9b) blood samples will be collected for participants in the Immunogenicity Subset only.
   Note: blood samples from participants *not* in the Immunogenicity Subset will be collected for potential future immunogenicity and safety assessments.
   Blood samples will be collected before the administration of study intervention on Days 1 and 29.
10. Before administration of study intervention, physical examination, medical history, pregnancy test for applicable participants, immunogenicity test, vital signs, contraindication to study intervention and elimination criteria will be assessed. At least 30 minutes after 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 and induration/swelling) and systemic events (fever, malaise/fatigue, myalgia, headache, nausea/vomiting and diarrhea) 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 whenever data are available.
14. For participants who withdraw from the study before Visit 9, an early termination visit should be completed by the participants as soon as possible.
    (14a) urine pregnancy test (beta-hCG) for female participants with childbearing potential will be performed if the early termination visit is performed within 30 days after the last administration of study intervention;
    (14b) blood samples for immunogenicity will only be taken if the early termination visit is performed at least 10 days after the previous blood sampling for immunogenicity. For participants *not* in the Immunogenicity Subset, blood samples will only be taken if the early termination visit is performed before Visit 7.

(14c) Solicited AEs will be collected if the early termination visit is performed within 7 days after the administration of study intervention.
(14d) 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

A new virus 2019-nCoV was identified as the causative agent of a worldwide outbreak of pneumonia-like respiratory disease since unexplained pneumonia cases in Wuhan, Hubei Province, China were reported in December 2019. Phylogenetic studies reported that the virus is 79% and 50% homological to severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), respectively (Lu et al. 2020), two previously identified coronaviruses that have also caused life-threatening respiratory disease worldwide. The virus was categorized in the betacoronavirus subfamily and thereafter re-named as SARS-CoV-2, and the disease caused by the virus became known as coronavirus disease 2019 (COVID-19) (Coronaviridae Study Group of the International Committee on Taxonomy of Viruses; WHO Situation Report-22).

As of early November 2020, more than 49 million confirmed cases and over 1 million deaths due to COVID-19 have been reported globally (WHO COVID-19 Weekly Epidemiological Update). In Taiwan, as of November 13, 2020, the number of confirmed cases was 597, with 7 deaths associated with COVID-19 (Taiwan CDC). 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 Interim Guidance 2020). In October 2020, the United States Food and Drug Administration (US FDA) approved the first treatment of remdesivir for COVID-19 under the Fast Track and Priority Review designations (FDA News Release 2020); a range of other therapies are currently in clinical trials (FDA CTAP 2020; WHO 2020). As governments, organizations, and healthcare experts worldwide endeavor to contain the spread of SARS-CoV-2 and care for those who are already infected and have developed COVID-19, there is a critical unmet need for prophylactic measures.

There is currently a global endeavor to develop vaccines against COVID-19 exploiting different technologies including messenger ribonucleic acid (mRNA), deoxyribonucleic acid (DNA), non-replicating viral vector, inactivated virus, and protein subunit (Rego et al. 2020).
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 also contains 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 currently no cure for the potentially lethal COVID-19. The availability of multiple vaccines represents a consolidated approach to augment anti-SARS-CoV-2 immunity. Vaccine coverage for the global population is an enormous challenge. Development of a range of vaccines will provide flexibility with prevention strategies should some of the licensed vaccines fail or lose effectiveness over time. Further, with multiple vaccines in the armament, mass vaccination programs could be accelerated. The current study will evaluate the safety, tolerability, and immunogenicity of the subunit vaccine MVC-COV1901 against SARS-CoV-2 in adult participants. Due to the highly contagious nature of SARS-CoV-2, partly due to

transmission via asymptomatically infected individuals, the prompt development of safe and effective vaccines are of utmost importance for regional and global public health.

2.2. Background

Subunit vaccines contain only the antigenic portion of the pathogen that is necessary to induce a protective immune response. A number of subunit vaccines against SARS-CoV and MERS-CoV are under development using the full-length S protein, the receptor binding domain (RBD), non-RBD S protein fragments, and non-S structural proteins (Wang et al. 2020). With 79.6% genomic sequence homology with SARS-CoV, the sequences encoding the open reading frame, 4 structural proteins consisting of S (spike), E (envelope), M (membrane), N (nucleocapsid), and 6 accessory proteins have been characterized (Zhou et al 2020).

The SARS-CoV-2 virus gains entry into the host cells through structural changes of the densely glycosylated S protein that allow fusion of the viral membrane with the host cell membrane, resulting in viral infection (Wrapp et al. 2020, Walls et al. 2020). The S protein of SARS-CoV-2 is a trimeric class I fusion protein that exists in a metastable prefusion conformation. It contains three segments: a large ectodomain, a transmembrane domain, and a cytoplasmic tail. The ectodomain consists of two functional subunits, an S1 subunit responsible for binding to the host cell receptor and an S2 subunit for fusion of the viral and cellular membranes (Belouzard et al. 2012). S1 subunit binds to the angiotensin-converting enzyme 2 (ACE2) receptors (Li et al. 2003; Zhou et al. 2020) which are expressed abundantly in lung and small intestine cells (Hamming et al. 2004).

To use an antigen with correct conformation is crucial for a vaccine to effectively generate antibody-mediated immune response. S protein has two major conformational states, prefusion and postfusion (Graham 2020). MVC-COV1901 consists of stabilized prefusion S 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 ACE2 and to induce high levels of neutralizing antibody (Pallesen et al. 2017; Wrapp et al. 2020). The neutralizing antibodies induced by S protein could block the binding of ACE2 receptors, hence inhibiting viral infection.

MVC-COV1901 is formulated with 2 adjuvants, namely CpG 1018 (a 22-mer CpG-enriched oligodeoxynucleotide [ODN] phosphorothioate) and $Al(OH)_3$. Upon internalization into the cells, the unmethylated CpG sequences are recognized as foreign by and bind to toll-like receptor 9 (TLR9), which is expressed in the plasmacytoid dendritic cells (pDCs) and B cells. This interaction activates the antigen presenting pDCs and B cells and 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). CpG ODN was shown to induce cytotoxic T cells response and enhance the antibody-mediated response to hepatitis B antigen in mice and in human when formulated with $Al(OH)_3$ (Davis et al. 1998; Cooper et al. 2004).

The safety of MVC-COV1901 was evaluated in a single- and repeat-dose toxicity studies in rats. In the dose range finding toxicity study with S-2P protein at tested doses 5 microgram (mcg), 25 mcg, and 50 mcg, formulated with either CpG 1018 or CpG 1018 in combination with $Al(OH)_3$, the test article was injected into rats via the intramuscular (IM) route either once in the single-dose study or twice (Days 1 and 15) in the repeat-dose study. The results showed that S-2P protein in the two adjuvant systems administrated intramuscularly 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. In the 4-week repeat-dose toxicity study of biweekly IM injection with a 4-week recovery phase in rats, MVC-COV1901 with 5 mcg, 25 mcg, and 50 mcg of S-2P protein was injected 3 times, once biweekly (Days 1, 15, and 29). 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.

Additionally, immunogenicity tests were conducted in mice administered 2 times (Days 1 and 22) with S-2P protein at low dose (1 mcg of S-2P per mouse), high dose (5 mcg of S-2P per mouse), and the corresponding adjuvant controls; blood samples were collected at pre-dose, Days 21 and 35 or 36. The immunogenicity of the rats immunized with two doses 50 mcg S-2P proteins combined with CpG 1018 alone or CpG 1018 plus $Al(OH)_3$ in single- and repeat-dose toxicity study described above were also evaluated; blood samples were collected pre-dose and at Day 29. The S-2P protein at both 1 mcg and 5 mcg, when formulated with combined CpG 1018 and $Al(OH)_3$, was able to induce higher neutralization antibody titers than when it is with each single adjuvant alone against both authentic SARS-CoV-2 and SARS-CoV-2 S pseudovirus. The neutralization antibody titers were also higher after the second immunization than after the first immunization. S-2P protein at 5 mcg formulated with the combined adjuvants was shown to have induced T helper type 1-skewed T cell responses after two-dose vaccination in the mouse model. Similar results were also observed in the rat model immunized with 50 mcg S-2P protein.

At the time of the finalization of this protocol CT-COV-21, the Phase I prospective study (protocol number CT-COV-11, NCT04487210) evaluating the safety and immunogenicity of MVC-COV1901 in Taiwanese adults aged ≥ 20 to < 50 years was still ongoing. Three dosages of S protein (5 mcg, 15 mcg, and 25 mcg) with adjuvant were chosen to be tested based on the immunogenicity and toxicology profiles observed in the nonclinical studies. The subjects received two doses of vaccines, on Day 1 and Day 29. Preliminary results showed that MVC-COV1901 was well tolerable and elicited immune responses in all subjects treated with two doses of 5 mcg, 15 mcg, or 25 mcg S-protein with adjuvant. None SAE/AESI occurred at the time of the finalization of this protocol CT-COV-21. The most frequent reported local solicited adverse event was pain, ranging from 73.3%~86.7% for all dosage groups; the second frequent local solicited event was induration, ranging from 6.7%~20% for all dosage groups. All of the local solicited events were mild in intensity. The most frequent reported systemic solicited event was malaise/fatigue, ranging from 13.3%~40.0% for all dosage groups; the second most frequent systemic solicited event was headache, ranging from 6.7%~13.3%. Most of the systemic solicited events were mild in intensity except for one malaise/fatigue in high dose group, which

was moderate in intensity. The seroconversion rate achieved both 100% 14 days post second vaccination in subjects treated with 15 mcg and 25 mcg.

A detailed description of the chemistry, pharmacology, safety, and immunogenicity of MVC-COV1901 is provided in the Investigator's Brochure (MVC-COV1901 Investigator's brochure, version 2.1, 23-OCT-2020).

2.3. Benefit/Risk Assessment

No clinical data with MVC-COV1901 were available at the time of the finalization of the CT-COV-21 protocol. More detailed information about the nonclinical information of MVC-COV1901 are available in the latest Investigator Brochure.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: MVC-COV1901		
Potential local injection site reactions (pain/tenderness, erythema/redness and induration/swelling) and systemic adverse events (AEs) (fever, malaise/fatigue, myalgia, headache, nausea/vomiting and diarrhea)	These reactions and AEs are commonly associated with vaccines (FDA CBER Guidance 2007). Injection of aluminum adjuvants often induces a local inflammatory 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%). According to the preliminary results from Phase I study of MVC COV1901, the most frequent reported local solicited adverse event was pain (73.3%-86.7%) and induration (6.7%-20%), the most frequent	This study includes the use of placebo which only consists of saline to monitor the possible AEs and/or abnormalities caused by S-2P protein and the adjuvants. 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. Injections site reactions and systemic AEs will be monitored within 7 days after each administration of study intervention.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	reported systemic solicited event was malaise/fatigue (13.3%-40.0%) and headache (6.7%-13.3%).	
Potential immune-mediated reactions, e.g. vaccine-associated enhanced disease (VAED), Guillain-Barré syndrome; other unknown AEs and laboratory abnormalities with a novel vaccine	No SAE/AESI/VAED defined in this protocol occurred in the ongoing Phase I study of MVC-COV1901 at the time of protocol finalization. Non-clinically significant changes were observed in nonclinical studies in mice and rats. These changes were considered to be related to the adjuvant. Vaccine-associated disease enhancement has been reported for respiratory syncytial virus, feline coronavirus, and Dengue virus vaccines.	This study includes the use of placebo which only consists of saline to monitor the possible AEs and/or abnormalities caused by S-2P protein and the adjuvants. 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. All participants are followed for SARS-CoV-2 antigen-specific immunoglobulin titers and SARS-CoV-2 neutralizing titers, and all laboratory-confirmed SARS-CoV-2 cases including severe cases.
Potential allergic reaction to vaccination	Although considered rare, allergic reaction to vaccination may occur, which causes rash, urticaria, or even anaphylaxis.	The study excludes participants who have a history of hypersensitivity to vaccines or allergic reactions to the components of MVC-COV1901.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
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. Blood sample is required only at screening for the purpose of eligibility assessment and at 4 other visits for immunogenicity test. 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

Benefits to individual participants may include:

- Receive a potentially efficacious COVID-19 vaccine and be protected from the disease.
- Access to medical evaluations associated with study procedures, such as clinical laboratory assessments, physical examination, and vital signs examination.
- 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.

2.3.3. Overall Benefit Risk Conclusion

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

3. Objectives and Endpoints

Objectives	Endpoints
Primary Safety	
To evaluate the safety and tolerability of MVC-COV1901 from Visit 2 (Day 1) to Visit 7 (28 days after the second dose of study intervention),	For all participants who receive at least one dose of study intervention, the safety and tolerability of MVC-COV1901 from Visit 2 (Day 1) to Visit 7 (28 days after the second dose of study intervention) in terms of the number and percentage of participants with the occurrence of: • Solicited local AEs (up to 7 days after each dose of study intervention) • Solicited systemic AEs (up to 7 days after each dose of study intervention) • Unsolicited AEs (up to 28 days after each dose of study intervention) • AE of special interest (AESI) • VAED • Serious adverse events (SAEs) Note: - Solicited local AEs: pain/tenderness, erythema/redness, induration/swelling - Solicited systemic AEs: fever, malaise/fatigue, myalgia, headache, nausea/vomiting, diarrhea
Primary Immunogenicity	
To evaluate the immunogenicity of MVC-COV1901, as compared to placebo, in terms of neutralizing antibody titers	For participants in the Immunogenicity Subset, the neutralizing antibody titers at Visit 7 (28 days after the second dose of study intervention) in terms of: • Geometric mean titers (GMT) • Seroconversion rate (SCR) • GMT ratio 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 - 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 over the study period	For all participants who receive at least one dose of study intervention, the safety of MVC-COV1901 within the whole study period in terms of the number and percentage of participants with the occurrence of: • ≥ Grade 3 AE • AESI • VAED • SAE
Secondary Immunogenicity	
To evaluate the lot-to-lot consistency of MVC-COV1901 in participants of the ≥ 20 to < 65 years age group	For participants in the ≥ 20 to < 65 years age group in the Immunogenicity Subset, the equivalence of the neutralizing antibody GMTs among 3 different lots of MVC-COV1901 at Visit 7 (28 days after second dose of study intervention)
To evaluate the immunogenicity of MVC-COV1901, as compared to placebo, in terms of antigen-specific immunoglobulin titers and neutralizing antibody titers	For all participants in the Immunogenicity Subset, the antigen-specific immunoglobulin titers and neutralizing antibody titers at Visit 4 (28 days after the first dose of study intervention), Visit 6 (14 days after the second dose of study intervention), Visit 7 (28 days after the second dose of study intervention) and Visit 9 (180 days after the second dose of study intervention) in terms of: • GMT • SCR • GMT ratio
Exploratory	
To estimate the efficacy of MVC-COV1901, as compared to placebo, in the prevention of COVID-19	For all participants who receive at least one dose of study intervention, • The number of laboratory-confirmed COVID-19 cases occurring ≥ 15 days after any dose of study intervention. • The number of laboratory-confirmed COVID-19 severe cases occurring ≥ 15 days after any dose of study intervention.

4. Study Design

4.1. Overall Design

This Phase II study is designed as follows:

- Prospective, placebo-controlled, double-blinded (investigator/site staff and participants; the Sponsor will be blinded until the interim analysis)
- Multi-center, multi-regional
- Approximately 3700 adult participants who are generally healthy or with stable pre-existing health conditions will be randomized. Taking into account an overall dropout rate of approximately 5%, a total of 3500 evaluable participants will be included for endpoints evaluation.
- Randomization of participants will be stratified by age, that is ≥ 20 to < 65 years and ≥ 65 years of age, with a minimum of approximately 20% of the participants are ≥ 65 years of age
- All eligible participants will be randomized to receive either MVC-COV1901 or placebo in a 6:1 ratio.
- Two parallel treatment arms as follows:
  a. Vaccine (MVC-COV1901): approximately 3180 participants will be randomized to receive 2 doses of MVC-COV1901 at 15 mcg of S-2P protein
  b. Placebo: approximately 530 participants will be randomized to receive 2 doses of placebo containing only saline
- Treatment dosage and route of administration: each participant will receive 2 doses of MVC-COV1901 or placebo, administered 28 days apart via IM injection in the deltoid region, preferably of the nondominant arm, at Visit 2 (Day 1) and Visit 4 (Day 29).
- The study consists of 6 on-site visits and 3 phone calls:
  - Day -28 to Day -1, Visit 1 (Screening)
  - Day 1, Visit 2 (First dose of study intervention)
  - Day 8 ± 2, Visit 3 (Phone call)
  - Day 29 ± 3, Visit 4 (Second dose of study intervention)
  - Day 36 ± 2, Visit 5 (Phone call)
  - Day 43 ± 3, Visit 6
  - Day 57 ± 3, Visit 7
  - Day 85 ± 3, Visit 8 (Phone call)
  - Day 209 ± 14, Visit 9

  Unscheduled visit(s) may be arranged when deemed necessary by the investigator or study medical monitor.
- The immunogenicity endpoints will be assessed in the participants of the Immunogenicity Subset only. 1090 randomized participants will be included in the Immunogenicity Subset: 820 randomized participants in the ≥ 20 to < 65 years age group will be included in the Immunogenicity Subset to evaluate immunogenicity and lot-to-lot consistency of MVC-COV1901; and 270 randomized participants in the ≥ 65 years age group will be included in the Immunogenicity Subset to evaluate immunogenicity of MVC-COV1901 (see Table 4-1).

- For participants *not* included in the Immunogenicity Subset, blood samples will be collected at Visit 2 (Day 1, before administration of study intervention) and Visit 7 (28 days after the second vaccination) for potential future immunogenicity and safety assessments.
- Participants of ≥ 20 to < 65 years of age in the Immunogenicity Subset will be randomized to receive either 1 of 3 lots of MVC-COV1901 or placebo in a 2:2:2:1 ratio (Lot 1:Lot 2:Lot 3:placebo).

Table 4-1 The approximate target number of populations and treatment ratio by age stratification

Age Group	Number of evaluable participants	Vaccine:Placebo ratio (evaluable participants)	Number of randomized participants in Immunogenicity Subset	Number of evaluable participants in Immunogenicity Subset
≥ 20 to < 65	2800	6:1 (2400:400 participants)	820*	767*
≥ 65	700	6:1 (600:100 participants)	270	256
Total	**3500**	**6:1 (3000:500 participants)**	**1090**	**1023**

* For lot-to-lot consistency analysis of MVC-COV1901. See Section 9.4 for details of sample size calculation.

- Total study duration per participant: approximately 237 days (28 days screening, 29 days treatment, 180 days follow-up)
- An Independent Data Monitoring Committee (IDMC) will review the accumulated safety data when the first 2000 participants have been followed up for at least 7 days after the first dose of study intervention and when they have been followed up for at least 7 days after the second dose of study intervention vaccination. Cumulative SAE data will be reviewed by the IDMC monthly to ensure the continuing safety of the participants. If 2 or more vaccine-related SAE occurs, the IDMC will meet to oversee the ethical and safety aspects of the study. The composition of the IDMC will be outlined in the IDMC Charter.
- An interim analysis of safety, immunogenicity, and lot-to-lot consistency will be carried out 1 month (28 days) after all participants have completed the second dose of study intervention *and* 2 months after half of the participants have completed the second dose of study intervention. At the time of interim analysis, the Sponsor (except for the safety monitoring team) will be unblinded, but the investigator/site staff and participants will remain blinded until study completion. Additional analyses to support discussion with the regulatory authority may be planned, if deemed appropriate.
- Subjects who continue in the study until Day 119 will be offered the option to enter an extension study (under a separate protocol: CT-COV-21e) if they meet an urgent condition and/or the investigator has to unblind the participant. Subjects who do not enter the extension study are encouraged to complete all subsequent visits.

- A subsidiary study (Protocol NO.: CT-COV-21s) will be conducted with a reduced number of study centers and subjects to evaluate the scaled-up MVC-COV1901 vaccine with manufacturing change.

4.2. Scientific Rationale for Study Design

This study is designed as a randomized, double-blind, placebo-controlled study to assess the safety and immunogenicity of the selected dose of MVC-COV1901 (see Section 4.3) in an expanded population. A placebo control is used to establish the magnitude of changes in safety and immunogenicity endpoints that may occur in the absence of the test product. Participants will be randomized to the 2 treatment arms before the first dose of study intervention to minimize bias in the assignment of participants to the vaccine group, although there is a higher ratio of assignment to vaccine. Randomization will also increase the possibility of balanced distribution of participants of various demography and baseline characteristics across treatment arms.

The treatment assignment is blinded to the investigator and participants throughout the study to reduce potential bias during data collection and evaluation of study endpoints. The Sponsor will also be blinded until the time of interim analysis (i.e. a timepoint upon which all participants have been administered both doses of study intervention), upon which they will be unblinded (except for the safety monitoring team) due to the need of communicating the study results with the regulatory authority for further strategic decision making. As the color of the study interventions in suspension are slightly different, i.e. opalescent for MVC-COV1901 after shaking and clear for placebo, blinding will be guaranteed by assigning unblinded qualified personnel who will be responsible for study intervention administration, handling dispensing log, and maintaining study intervention accountability (Section 6.2).

The study considers a diverse population by including elderly participants of 65 years old and older, and participants with stable pre-existing health conditions to help ensure that the vaccine is safe for the indicated populations. The safety of the participants, especially the indicated populations, is ensured by implementing different measures of safety monitoring, including the inclusion of a IDMC to review safety data regularly throughout the study and the examination of all participants for any contraindication to the study intervention before and after each dose of study intervention. As no safety data are available to support the use of the study intervention on high risk participants or those with comorbidities, such as participants with immunosuppressive illness, abnormal liver function, and autoimmune diseases, these participants and females who are pregnant or breast-feeding will be excluded from the current study.

The analysis endpoints in this study are similar to the endpoints for other preventive vaccine trials for infectious diseases. In the safety analysis, solicited AEs will be collected for 7 days after each dose of study intervention, a period that has proven adequate to describe reactogenicity events in previous vaccine studies. Additionally, unsolicited AEs will be collected for 28 days after each dose of study intervention. Throughout the study, ≥ Grade 3/severe AE, AESI, VAED, and SAE will be collected. AESIs include the immune-mediated AESIs as included in the HEPLISAV-B® post hoc analysis (Hyer et al. 2018; Appendix 4, Section 10.4) whereas VAEDs include AESIs relevant to COVID-19 identified by the Brighton Collaboration (SPEAC 2020; Appendix 5, Section 10.5). VAED has been described in nonclinical models for

SARS and MERS in which candidate vaccines induced non-neutralizing antibody and a T helper type 2-biased immune response, but similar risk in human is not known (Deming et al. 2006; Bolles et al. 2011; Honda-Okubo et al. 2015; Agrawal et al. 2016; Houser et al. 2017). The study also explores the efficacy of MVC-COV1901 by collecting data of all laboratory-confirmed COVID-19 cases in treated participants from Day 1 throughout the study period. Data beginning from ≥ 15 days after any dose of study intervention will be analyzed, with the main focus on the efficacy from ≥ 15 days after the second dose of study intervention, which is the time period considered necessary for the vaccine to induce a protective immune response.

4.3. Justification for Dose

The S-2P protein doses tested in single- and repeat-doses toxicity and immunogenicity studies with the combination of CpG 1018 and $Al(OH)_3$ as adjuvants in animal models and the preliminary results from the ongoing Phase I clinical study (protocol number CT-COV-11, NCT04487210) are described in Section 2.2. Briefly, S-2P protein at 5, 25, and 50 mcg did not cause any significant adverse effects in the tested animals, and when formulated with combined CpG 1018 and $Al(OH)_3$ could induce high level of neutralization antibody titers. The maximum dose of S-2P protein intended for clinical setting is 25 mcg. Based on the toxicology and immunogenicity profile of the vaccine in the nonclinical studies, 3 dose levels (5, 15, and 25 mcg) of S-2P protein in MVC-COV1901 were chosen to be tested in the Phase I clinical study. The preliminary results from this Phase I study showed that MVC-COV1901 was well tolerable in all subject groups treated with two doses of 5 mcg, 15 mcg, and 25 mcg S-protein with adjuvant. The seroconversion rate achieved 100% in subjects received two doses of either 15 mcg or 25 mcg S-2P protein.

In this Phase II study, 15 mcg of S-2P protein is selected as the dose to be tested.

4.4. 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 ≥ 20 to < 65 years, or ≥ 65 years of age at randomization.
2. Healthy adults or adults with pre-existing medical conditions who are in stable condition. 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 participant must:
    a. Be either 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. Or, if of childbearing potential, be abstinent or agree to use medically effective contraception from 14 days before screening to 30 days following the last injection of study intervention. Acceptable forms include:
        i. Implanted hormonal methods of contraception or placement of an intrauterine device or intrauterine 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
    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 has not travelled overseas within 14 days of screening and will not have any oversea travelling throughout the study period.
6. 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 applies:

1. Pregnant or breast feeding or have plan to become pregnant in 30 days after last administration of study intervention.
2. Employees at the investigator's site, of the Sponsor or the contract research organization (CRO) 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

Medical Conditions

9. Immunosuppressive illness or immunodeficient state, including hematologic malignancy, history of solid organ, bone marrow transplantation, or asplenia.
10. A history of autoimmune disease (systemic lupus, rheumatoid arthritis, scleroderma, polyarthritis, thyroiditis, Guillain-Barré syndrome, etc.).
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 injection or phlebotomy.
13. Human immunodeficiency virus (HIV) antibody positive participants with CD4 count < 350 cells/mm^3 or a detectable HIV viral load within the past year (low level variations from 50-500 viral copies/mL or equivalent which do not lead to changes in antiretroviral therapy [ART] are permitted).
14. Hepatitis B surface antigen (HBsAg) positive participant with positive hepatitis B e antigen (HBeAg) or abnormal liver function.
15. Hepatitis C virus (HCV) antibody positive participants with detectable HCV ribonucleic acid (RNA) viremia in recent 12 weeks.
16. Participant with ongoing acute diseases or serious medical conditions which will interfere with adherence to study requirements, or the evaluation of any study endpoint.
    Acute diseases or serious medical conditions include cardiovascular (e.g. New York Heart Association Grade III or IV), pulmonary (e.g. chronic obstructive pulmonary disease stage III or IV), hepatic (e.g. Child-Pugh Class C), neurologic (e.g. dementia), metabolic (e.g. diabetes mellitus with hemoglobin A1c [HbA1c] > 8%), renal (Stage 3 or worse chronic kidney disease), psychiatric condition (e.g. alcoholism, drug abuse), current severe infections, medical history, physical findings, or laboratory abnormality that in the investigators' opinion are not in stable condition and participating in the study could adversely affect the safety of the participant.

17. Participant with previous known or potential exposure to SARS-CoV-1 or 2 viruses (EXCEPT for those who have been tested negative and completed the 14-day self-managements/ home quarantines/ home isolations) or received any other COVID-19 vaccine.
18. Participant with 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.
19. 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. Restriction 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 another 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 on 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 (not including any coronavirus vaccine other than study intervention, which is prohibited)
- Administration of any live-attenuated vaccine within 28 days before the *first* dose of study intervention (not including any coronavirus vaccine other than study intervention, which is prohibited)

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	Placebo
Type	Vaccine	Placebo
Dose Formulation	Recombinant S-2P protein formulated with 750 mcg CpG 1018 and 375 mcg aluminum hydroxide in suspension	Saline
Unit Dose Strength(s)	15 mcg of S-2P protein/0.5 mL	None, Saline/0.5 mL
Dosage Level(s)	15 mcg of S-2P protein, 2 doses at 28 days apart	2 doses at 28 days apart
Route of Administration	IM injection	IM injection
Use	Experimental	Placebo
IMP or NIMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labeling	Study intervention will be provided in pre-filled syringe. Each syringe will be labeled as required per country requirement.	Study intervention will be provided in pre-filled syringe. Each syringe will be labeled as required per country requirement.

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

Table 6-2 Study Arm(s)

Arm Title	Vaccine (MVC-COV1901)	Placebo
Arm Type	Experimental	Placebo
Arm Description	Participants will receive 2 doses of vaccine containing 15 mcg of S-2P protein, administered 28 days apart via IM injection at Visit 2 (Day 1) and Visit 4 (Day 29)	Participants will receive 2 doses of placebo, administered 28 days apart via IM injection at Visit 2 (Day 1) and Visit 4 (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 an 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 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 Harmonisation 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 study intervention will be supplied ready for use by the Sponsor to the study sites. No further preparation will be needed before the administration of study intervention.

The investigator will assign unblinded qualified 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 the study intervention 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 the study intervention and only the assigned unblinded personnel may supply or administer 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

All eligible participants will be randomized to receive either MVC-COV1901 or placebo in a 6:1 ratio. Randomization will be stratified based on age (≥ 20 to < 65 years and ≥ 65 years, a minimum of approximately 20% of the participants will be ≥ 65 years of age). 1090 randomized participants (820 participants in the ≥ 20 to < 65 years age group and 270 in the ≥ 65 years age group) will be the Immunogenicity Subset and those aged ≥ 20 to < 65 years will be randomized to 3 different lots of MVC-COV1901 vaccine and to placebo in a 2:2:2:1 ratio.

All participants will be centrally assigned to randomized study intervention using an interactive web response system (IWRS). Before the study is initiated, the log-in information and directions for the IWRS will be provided to each site.

6.3.2. Blinding

This is a double-blind study in which participants and investigators are blinded to study intervention. The IWRS will be programmed with blind-breaking instructions. In case of an emergency or urgent condition other than safety events (i.e. on request from participants with high risk of acquiring and transmitting infection), 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 that for the unblinding must be recorded.

The IDMC will review the safety data in the blinded manner. The IDMC and/or Sponsor (except for the safety monitoring team) may unblind the intervention assignment for any participant with an 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.

For the interim analysis, an independent, unblinded team of the CRO consisting of personnel representing relevant functions including statistical, programming, and report writing, will be involved in the activity of the interim analysis; all activities of the unblinded team will be separated from the main blinded team of the study. The Sponsor will be blinded until the time of the interim analysis. As MVC-COV1901 and placebo are visually distinct in their color of appearance, the investigator will assign unblinded qualified 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 in all other study staff and the participants.

If the participant is unblinded due to urgent condition other than safety events, subsequent safety visits will be identical from those of participants remained in the main study. But immunogenicity and safety data collected from unblinded participants will be analyzed separately.

Participants who continue in the study until Day 119 will be offered the option to enter an extension study (under a separate protocol: CT-COV-21e) if they meet an urgent condition and/or the investigator has to unblind the participant. Participants who do not enter the extension study are encouraged to complete all subsequent visits. Participants who are unblinded and decide to join the extension study (CT-COV-21e) will be withdrawn from this main study analysis.

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 unblinded qualified 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. All therapies taken by participant prior to screening and during the study will be recorded on the appropriate page of the electronic case report form (eCRF). 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
- Major surgeries will be recorded within 5 years prior to the first dose of study intervention until EOS
- 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.

6.8.1. Prohibited Therapy/Medication

The following therapies 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
- Administration of any coronavirus vaccines other than study intervention.

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 further dose of study intervention if any of the following 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). Any coronavirus vaccine other than study intervention is prohibited throughout the study.
- 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 8.2.9)
- Any vaccine-related SAE during the study period

If study intervention is discontinued, the participant 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).

7.1.1. Contraindication to Study Intervention

Prior to each administration of study intervention at Visit 2 (Day 1) and Visit 4 (Day 29), participants will be assessed for criteria of contraindication 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:

- 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 (not including any coronavirus vaccine other than study intervention, which is prohibited)
- Any live-attenuated vaccine within 28 days before each dose of study intervention (not including any coronavirus vaccine other than study intervention, which is prohibited)
- Any condition that is a contraindication to study intervention based on the judgement of the investigator

In circumstances that participants could not be rescheduled for administration of study intervention within the visit window, they will still be encouraged to complete all 2 doses of study intervention, and the out-of-visit-window administration of study intervention will be recorded on the eCRF.

7.2. Participant 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 elimination 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 (Appendix 1, Section 10.1.9)

If a participant decides to join the extension study (CT-COV-21e) as described in Section 6.3.2, he/she has to withdraw from the main study.

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 eCRF. 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 him/her to obtain further safety information and to inform him/her 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 and new or ongoing AEs.

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

8.1. Safety Assessments

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

8.1.1. Demographics and Medical History

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

Medical history of each participant will be collected at screening and recorded on the Medical History eCRF page. Any significant medical conditions that are present prior to the start of study intervention will also be included in the Medical History eCRF 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.

8.1.2. 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 Visits 2, 4, 6, 7, 9 (Days 1, 29, 43, 57, 209), and at any unscheduled visit as required by the investigator if there is any indication of change in the participant's health since the previous visit. Physical examination scheduled for Visits 2 and 4 will be performed before 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 eCRF. Any clinically significant change from before the first dose of study intervention should be recorded as an AE.

8.1.3. Vital Signs

Vital signs will be measured at screening, at Visits 2 and 4 (Days 1 and 29) before administration of study intervention and approximately 30 minutes after 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 eCRF. The investigator will review all vital sign values for clinical significance. Additional vital signs will be obtained when clinically indicated. Any clinically significant change from before the first dose of study intervention should be recorded as an AE.

8.1.4. 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 reference point for the evaluation of AEs during the study, if needed. The protocol-required laboratory tests are as defined in Appendix 2 (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 local laboratory and in accordance with SOP or laboratory manual. All results of the safety laboratory measurements will be reported to the investigator and must be recorded in the eCRF.

8.1.5. Electrocardiography

Electrocardiography (ECG) will be performed before the subject receives the first study intervention and at any unscheduled visit as required by the investigator. The baseline ECG will

provide a reference point for the evaluation of AEs during the study, if needed. The assessment of whether the ECG is normal or abnormal should be recorded.

Abnormal ECG 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.

The results of ECG will be reported to the investigator and must be recorded in the eCRF.

8.1.6. Diary Card

Participants will be given a diary card at Visits 2 and 4 (Days 1 and 29) after administration of study intervention and must be instructed to record any solicited local and systemic AEs, unsolicited AEs, and concomitant medication.

The following local AEs will be solicited: pain/tenderness, erythema/redness, induration/swelling; and the following systemic AEs will be solicited: fever, malaise/fatigue, myalgia, headache, nausea/vomiting, and diarrhea (see Section 8.2.5). 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 8.2.5.1, and whether medication was taken to relieve the events. In the diary card, 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. A phone call visit will be made by a study staff to review the collected events at Visits 3 and 5 (Days 8 and 36). Any solicited AE that is ongoing beyond Day 8 will be recorded in the diary card until resolution. AEs recorded in the diary card beyond Day 8 after each dose of study intervention should be reviewed by study staff at the next study site visit. Participants will be required to return the diary card at Visits 4, 6 and 7 (Days 29, 43 and 57).

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 diary card. The collected information should be documented in the source documents and the information entered in the eCRF.

8.1.7. Pregnancy Testing

A urine pregnancy test for participants of childbearing potential will be performed at screening, before each dose of study intervention at Visit 2 (Day 1) and Visit 4 (Day 29), Visit 6 (Day 43), Visit 7 (Day 57), and any unscheduled visit as required by the investigator to establish the absence of pregnancy at any time during the participant's participation in the study.

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

The definitions of AEs and SAEs can be found in Appendix 3 (Section 10.3.1 and Section 10.3.2).

The definitions of unsolicited and solicited AEs can be found in Section 8.2.5 and further information is provided in Appendix 3 (Section 10.3.1).

AEs will be reported by the participant or, when appropriate, by the participant's legally authorized representative.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs including SAEs, AESI, VAED, 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, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3.3).

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

All solicited AEs will be collected within 7 days after each dose of study intervention. All unsolicited AEs will be collected within 28 days after each dose of study intervention.

All ≥ Grade 3/severe AEs, AESI, VAED, and SAEs will be collected from the start of study intervention until the end of 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.

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3 (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.

8.2.2. Method of Detecting AEs and SAEs

For solicited and unsolicited AEs, participants will be instructed to detect and record the AEs in a diary card (Section 8.1.6). 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, had any accidents, used any new medications, or changed concomitant medication regimens.

8.2.3. 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/contacts. All AEs including ≥ Grade 3/severe AEs, SAEs, AESI (Section 8.2.6), VAED (Section 8.2.7) 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 Appendix 3 (Section 10.3.3).

8.2.4. 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 suspected adverse reaction as soon as possible, but in no case 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.

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. Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

8.2.5. Solicited and Unsolicited Adverse Events

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
- *Systemic events*: fever, malaise/fatigue, myalgia, headache, nausea/vomiting, and diarrhea

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

8.2.5.1. 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 8-1 and Table 8-2, respectively, below.

Table 8-1 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

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 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 and per investigator's judgement.

Table 8-2 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#

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 and per investigator's judgement.

Intensity of unsolicited AEs will be assessed based on the classification of all AEs other than solicited AEs as described in Section 8.2.8.

8.2.5.2. 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 8.2.8.

8.2.6. 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 of this study are defined in Appendix 4 (Section 10.4). All AESIs will be recorded in the eCRF.

The investigator will report to the Sponsor or delegate any occurrence of AESI 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, reporting should follow the process of SAE reporting as described in Section 8.2.4 and indicate it as an AESI in the SAE/AESI/VAED reporting form.

8.2.7. Vaccine-associated Enhanced Disease

VAEDs will be collected according to the timepoints specified in the SoA (Section 1.3). VAEDs of this study are defined in Appendix 5 (Section 10.5). All VAEDs will be recorded in the eCRF.

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. If the VAED is also an SAE, reporting should follow the process of SAE reporting as described in Section 8.2.4 and indicate it as a VAED in the SAE/AESI/VAED reporting form.

8.2.8. Assessment of Intensity and Causality of AEs and SAEs

Intensity of AEs and SAEs

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 8-3). 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 (Appendix 3, Section 10.3.2), not when it is rated as severe.

Table 8-3 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, e.g. use of antibiotics to treat infection, other etiological treatment instead of symptomatic relief.
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 and per investigator's judgement.

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

Causality of AEs and SAEs

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 each AE/SAE. The investigator will use clinical judgment to determine the relationship. The investigator will also consult the Investigator's brochure and/or product information, for marketed products, in his/her assessment. For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/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 make an assessment of 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 following assessment of the causality of AE/SAE will be applied in the study:

Table 8-4 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.

8.2.9. Pregnancy

Details of all 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

Section 8.2.4. 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).

8.3. Immunogenicity Assessments

8.3.1. Antigen-specific Immunoglobulin Titers

Blood samples will be collected from all participants according to the SoA (Section 1.3). For participants in the Immunogenicity Subset (see Table 4-1), blood sampling will be performed at Visits 2, 4, 6, 7, and 9 (Day 1, 29, 43, 57, and 209); for participants not included in the Immunogenicity Subset, blood sampling will be performed at Visits 2 and 7 (Days 1 and 57). On Visit 2 (Day 1) and Visit 4 (Day 29), blood samples for immunogenicity test will be collected before administration of study intervention.

Antigen-specific immunoglobulin titers to S-2P protein will be evaluated in blood (serum) samples collected from participants in the Immunogenicity Subset. The detection and characterization of antigen-specific immunoglobulin will be performed by a central laboratory using a validated enzyme-linked immunosorbent assay (ELISA) method.

The actual time and date of each sample collected will be recorded in the eCRF, and unique sample identification 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.

8.3.2. Anti-SARS-CoV-2 Neutralizing Antibody

Blood samples collected from participants as described in Section 8.3.1 may also be used to measure the anti-SARS-CoV-2 neutralizing antibody titers by pseudovirus and/or live virus neutralization assays. The detection and characterization of neutralizing antibodies will be performed by central laboratories using validated pseudovirus and/or live virus neutralization assays.

8.4. Exploratory Efficacy Assessments

Efficacy of MVC-COV1901 will be assessed in all treated participants in an exploratory manner through self-reported laboratory-confirmed COVID-19 cases occurring starting from 15 days after any dose of study intervention.

Information of suspected COVID-19 will be collected at each visit. In circumstances when a participant meets the reporting requirements for COVID-19 (Appendix 6, Section 10.6.1; for severe cases, see Section 10.6.2), the study staff will instruct the participant to contact the designated national healthcare organization, e.g. Central Epidemic Command Center (CECC), for the follow-up action or procedures. The applicable local guideline should be followed for the clinical management of suspected and confirmed cases, e.g. molecular diagnostic, isolation of infected participants in a health facility and any treatment for infected participants.

Participants who have laboratory-confirmed SARS-CoV-2 infection should contact the study staff at their earliest convenience to inform of their medical conditions. Contact with the study staff could also be made by the participant's legal representative or family member 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 inform of their conditions.

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

Any participant who has confirmed SARS-CoV-2 infection and/or develop symptomatic COVID-19 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 eCRF.

8.5. Biological Samples

8.5.1. Blood Samples

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

Table 8-5 The Timepoint of Blood Samples Collected for the Study

Purpose of sample collection	Number of timepoints	Additional timepoints for Immunogenicity Subset
Screening laboratory safety tests (including hematology, biochemistry, immunology, serology)	1	-
Immunogenicity (serum antigen-specific immunoglobulin, anti-SARS-CoV-2 neutralizing antibody)	2	3

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

8.5.2. Urine Sample

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

8.6. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.7. Genetics

Genetics parameters are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

9. Statistical Considerations

The statistical analysis plan (SAP) will be finalized prior to database lock and unblinding and it will include a more technical and detailed description of the statistical analyses described in this section.

9.1. Statistical Hypotheses

The primary objective of this study is the assessment of the safety, tolerability, and immunogenicity of MVC-COV1901 which will be analyzed descriptively.

Equivalence testing for lot-to-lot consistency will be performed (see Section 9.3.5.1).

9.2. Analysis Sets

Analysis sets	Description
Randomized	All participants who are assigned a randomization number in the IWRS, 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 group corresponding to the study intervention that they actually receive.
Immunogenicity Subset	1090 randomized participants (820 participants in the ≥ 20 to < 65 years age group and 270 in the ≥ 65 years age group) who receive at least one dose of study intervention, have a valid immunogenicity test result prior to the first dose of study intervention and have at least one valid immunogenicity result post study intervention. Participants will be analyzed according to the group corresponding to the study intervention that they actually receive.
Per protocol Immunogenicity (PPI) Subset	Evaluable participants in the Immunogenicity Subset who receive the planned doses of study intervention, have a valid immunogenicity result at Visit 7, and who do not have a major protocol deviation that are 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.
Full Analysis Set (FAS)	All randomized participants who receive 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 group to which they are randomized.
Per protocol Set (PPS)	Participants in the FAS who receive the planned doses of randomized study intervention per schedule and who do not have a major protocol deviation that are 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.

9.3. Statistical Analyses

9.3.1. General Considerations

All measured variables and derived parameters will be listed by participant and tabulated by descriptive statistics. Summary descriptive statistics will be provided for all safety, immunogenicity, exploratory efficacy, and baseline/demographic variables. Data of all study sites and regions will be pooled for statistical analysis. In general, tabulation of results will be displayed by visit and by treatment arm.

Continuous variables will be summarized descriptively with number of participants, mean, median, standard deviation (SD), interquartile range (IQR), range (minimum and maximum), and 95% confidence interval (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 the baseline for the respective endpoints. 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 LoD, the value will be replaced by half of the LoD.

Significance tests (2-tailed, alpha = 0.05) without alpha adjustment will be performed for pairwise comparison where appropriate and *P*-value will be rounded to four decimal places, if applicable.

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 Safety Analysis

The primary safety analysis will be performed on the Safety Set.

The primary safety endpoints of study intervention include the occurrence rate of solicited (local and systemic) AEs, unsolicited AEs, AESI, VAED, and SAE from Visit 2 (Day 1) to Visit 7 (28 days after second dose of study intervention).

All AEs (except solicited AEs) will be coded as system organ class (SOC) and preferred term (PT) by the most updated Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of participants will be to summarize and tabulated for each treatment arm. In addition, the 95% CI of the percentage of participants will be calculated for the overall summary AEs.

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

The intensity and causality of the AEs will be summarized descriptively for each treatment arm.

9.3.3. Primary Immunogenicity Analysis

The primary immunogenicity analysis will be performed primarily on the PPI Subset. The same analysis will also be performed on the Immunogenicity Subset.

The primary immunogenicity endpoints of study intervention include the GMT, SCR, and GMT ratio of neutralizing antibody titers at Visit 7 (28 days after second dose of study intervention).

Seroconversion is defined as at least 4-fold increase of post-study intervention antibody titers from the baseline titer or from half of the LoD if undetectable at baseline. GMT ratio is defined as geometric mean of fold increase of post-study intervention titers over the baseline titers.

GMT is the geometric mean of the antibody titers of all participants in each treatment arm and will be calculated as follows:

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

GMT ratio = $\frac{GMT_{post-vaccination}}{GMT_{baseline}}$

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 or Wilcoxon rank-sum test. 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 median of ln(X) will also be presented.

For SCR, chi-square or Fisher's exact test will be used to perform comparison of the two treatment arms. 95% CI of the SCR will also be presented. Pearson's Chi-square test will be used except for the case of small cell count (less than 5).

9.3.4. Secondary Safety Analysis

The secondary safety analysis will be performed on the Safety Set.

The secondary safety endpoints of study intervention include the occurrence rate of ≥ Grade 3 AE, AESI, VAED, and SAE over the whole study period.

An overview of the number of events, number and percentage of participants who experience ≥ Grade 3 AE, related ≥ Grade 3 AE, AESI, VAED, SAE, related SAE, AE leading to discontinuation of study intervention, AE leading to study withdrawal, and death will be summarized by treatment arm and the total. All individual AESI, VAED, SAE, AE leading to discontinuation of study intervention, AE leading to study withdrawal, and death will be listed separately.

All AEs will be coded as SOC and PT by the most updated MedDRA. The number and percentage of participants will be summarized and tabulated for each treatment arm. The intensity and causality of the AEs will be summarized descriptively for each treatment arm. In addition, the 95% CI of the percentage of participants will be calculated for the overall summary AEs.

9.3.5. Secondary Immunogenicity Analysis

9.3.5.1. Lot-to-lot Consistency

The lot-to-lot consistency analysis will be performed primarily on the PPI Subset for the ≥ 20 to < 65 years age group. The same analysis will also be performed on the Immunogenicity Subset for the ≥ 20 to < 65 years age group.

The GMT of neutralizing antibody titers at Visit 7 (28 days after second dose of study intervention) will be estimated using Student's t-distribution.

Pairwise GMT ratio (with two-sided 95% CI) between the three lots (i.e. Lot 1 to 2, Lot 1 to 3, and Lot 2 to 3) will be evaluated by back transforming the mean difference and its 95% CI on the Log_e-transformed scale computed from the Student's t-distribution.

Equivalence among the 3 lots will be demonstrated if for each pair of lots, the two-sided 95% CIs of the GMT ratio is entirely within 0.5 and 2.0.

9.3.5.2. Antigen-specific Immunoglobulin Titers and Neutralizing Antibody Titers

The secondary immunogenicity analysis will be performed primarily on the PPI Subset. The same analysis will also be performed on the Immunogenicity Subset.

The secondary immunogenicity endpoints of study intervention include the GMT, SCR, and GMT ratio of antigen-specific immunoglobulin titers and neutralizing antibody titers at Visit 4 (28 days after the first dose of study intervention), Visit 6 (14 days after the second dose of study intervention), Visit 7 (28 days after the second dose of study intervention) and Visit 9 (180 days after the second dose of study intervention).

Refer to Section 9.3.3 for the statistical method for the specified variables.

9.3.6. Exploratory Endpoints Analyses

9.3.6.1. Exploratory Efficacy Analysis

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

The efficacy will primarily be analyzed for the number and percentage of participants with laboratory-confirmed symptomatic COVID-19 cases (all cases and severe cases) occurring starting from ≥ 15 days after administration of any dose of study intervention, and will be summarized for each treatment arm. The number and percentage of participants of all laboratory-confirmed cases including symptomatic COVID-19 and asymptomatic SARS-CoV-2 infection will also be summarized.

The definition of laboratory-confirmed COVID-19 case by Taiwan Centers for Disease Control, (Section 10.6.1) is:

Meet laboratory diagnosis criteria which is one or more of the following:

(1) Pathogen (SARS-CoV-2) isolated and identified from a clinical specimen (nasopharyngeal swab, throat swab, expectorated sputum, or lower respiratory tract aspirates).
(2) Positive molecular biological testing for viral (SARS-CoV-2) RNA from a clinical specimen (nasopharyngeal swab, throat swab, expectorated sputum, or lower respiratory tract aspirates).

9.3.7. Subgroup Analyses

For the safety endpoints and secondary immunogenicity endpoint (antigen-specific immunoglobulin titers and neutralizing antibody titers), subgroup analysis will be performed for the ≥ 20 to < 65 years and ≥ 65 years age groups. Subgroup analyses for other endpoints or other newly defined subgroup deemed relevant may also be performed, which will be detailed in the SAP. The statistical analysis method for the subgroup analysis will be provided in the SAP.

In case of an emergency or urgent condition other than safety events (i.e. on request from participants with high risk of acquiring and transmitting infection), the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Immunogenicity and safety data collected from unblinded participants will be analyzed separately as a post-hoc analytic set.

9.3.8. Interim Analysis

The safety, immunogenicity and lot-to-lot consistency data will be analyzed in an interim analysis when the following condition is met: 1 month (28 days) after all participants have completed the second dose of study intervention *and* 2 months after half of the participants have completed the second dose of study intervention. The results of the interim analysis will be used for regulatory decision making. At the time of interim analysis, the Sponsor (except for the safety monitoring team) will be unblinded, but the investigator/site staff and participants will remain blinded until study completion.

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 and report to the Sponsor will be unblinded to the individual treatment group assignments. Interim analysis results will not be shared with investigators, participants, or the study team who are involved in the conduct of the study before the final database lock.

The analysis method for the safety and immunogenicity endpoints described above will be used for the interim analysis. The SAP will describe the planned interim analyses in greater detail.

9.4. Sample Size Determination

Approximately 3700 participants will be randomly assigned to study intervention to achieve 3500 evaluable participants after considering 5% dropout rate. The total sample size, the sample size of each age subgroup, and of each treatment arm are based on the minimum requirement for a Phase II vaccine study as agreed with the Taiwan FDA.

Lot-to-lot consistency will be analyzed in the ≥ 20 to < 65 years group of the Immunogenicity Subset only. For calculating the sample size of lot-to-lot consistency, the statistical methodology is based on the use of a two-sided 95% CI [100(1-2α)%], calculated using the differences of the post-vaccination GMT of neutralizing antibody titers between pairs of lots.

H_{0i}: $\frac{GMT(i)}{GMT(j)} \leq 0.5$ or $\frac{GMT(i)}{GMT(j)} \geq 2$

vs.

H_{1i}: $0.5 < \frac{GMT(i)}{GMT(j)} < 2$

Where i = 1, 2, 3 and j = 2, 3, 1

Since there are 3 lots for the hypothesis testing, the overall power will be (individual power)^3.

For each of the above scenarios, the sample size estimation was performed under the following assumptions as defined in the study outline:

- Level of significance = 0.025 (one-sided)
- Level of individual power = 0.966 (Overall power = 0.901)
- Two one-sided tests (TOST) Margin = 0.5, 2
- Expected GMT ratio = 0.55, 0.56, and 0.57
- Common Coefficient of Variation (CV) = 0.31, 0.32, and 0.33
- Primary test = TOST
- Dropout rate = 6.4% of the original sample size

Table 9-1 Sample Size Calculation for Lot-to-Lot Consistency

GMT ratio	CV	Sample size per lot	Total sample size (assume the ratio of lot 1-3 and placebo group = 2:2:2:1)	Total Sample size after accounting for 6.4% drop out rate
0.55	0.31	291	1019	1089
0.55	0.32	309	1082	1156
0.55	0.33	328	1148	1227
0.56	0.31	206	721	771
0.56	0.32	219	767	820
0.56	0.33	232	812	868
0.57	0.31	155	543	581
0.57	0.32	164	574	614
0.57	0.33	174	609	651

CV = coefficient of variation; GMT = geometric mean titer

Table 9-2 Power Calculation

Total sample size considering 6.4% dropout rate	Sample size (per lot)	Assumed True GMT Ratio	Assumed CV	Overall Power
N = 820	N = 219	0.56	0.32	0.9024
			0.35	0.8197
			0.45	0.4872
			0.55	0.2545
			0.65	0.1352
		0.6	0.32	>0.995
			0.35	>0.995
			0.45	0.9800
			0.55	0.8829
			0.65	0.7139
		0.65~1.5	0.32~0.65	>0.98
		1.6	0.32	>0.995
			0.35	>0.995
			0.45	>0.995
			0.55	0.9849
			0.65	0.9276
		1.7	0.32	>0.995
			0.35	>0.995
			0.45	0.9320
			0.55	0.7536
			0.65	0.5424

CV = coefficient of variation; GMT = geometric mean titer

Under the assumption of achieving an overall power of 90%, alpha level of 0.025, GMT ratio of 0.56, and CV of 0.32 (Table 9-1), an evaluable sample size of 219 per lot is required. Assuming

the true GMT ratio between lots is within 0.65 to 1.5 and CV within 0.32 to 0.65, the selected number of 219 participants per lot could achieve an overall power of 98% (Table 9-2) to demonstrate lot-to-lot consistency by ruling out a less than 0.5-fold or a larger than 2.0-fold in GMT ratio. The shaded rows in Table 9-2 indicate scenarios of various GMT ratio between two lots for which the study sample size provides at least 90% power.

Therefore, a total of 767 evaluable participants will be required with the 2:2:2:1 ratio for lots 1 to 3 and placebo. Taking into account 6.4% dropout rate, a total of 820 participants will be enrolled for the lot-to-lot equivalence analysis.

Taking reference from the calculation above and considering the minimum 20% threshold, approximately 256 evaluable participants of ≥ 65 years of age will be included (219 receiving vaccine, 37 receiving placebo) in the Immunogenicity Subset. Taken together, the calculated sample size of the lot-to-lot consistency analysis in the ≥ 20 to < 65 years group and the estimated sample size of ≥ 65 years group constitutes the total evaluable participants in the Immunogenicity Subset.

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 GCP guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, investigator's brochure, and other relevant documents (e.g. 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 ICH guidelines, the IRB/IEC, 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 representatives 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 another 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 or delegate. 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. The accumulated safety data will be reviewed by the IDMC at a designated time point and SAE data at regular interval. 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 monitor the safety 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 electronic CRFs unless transmitted to the Sponsor or delegate electronically (e.g. laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided by the Sponsor or delegate.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy, including definition of study critical data items and processes (e.g. risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- 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 (e.g. 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 first act of recruitment is the first participant in and will be the study start date.

Study/Site Termination

The Sponsor or delegate 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 or delegate 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.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 10-1 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- 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), Aspartate aminotransferase (AST), Sodium (Na), Potassium (K), Chloride (Cl)
Immunology	Antinuclear antibody (ANA), Anti-double stranded deoxyribonucleic acid (dsDNA) antibody, Anti-neutrophil cytoplasmic antibodies (ANCA, including cytoplasmic ANCA [c-ANCA], perinuclear ANCA [p-ANCA]).
Serology	Anti-HIV antibody or rapid test, HBsAg, HBeAg, Anti-HCV antibody

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.
Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g. electrocardiogram, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e. 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 <u>NOT</u> 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 • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition • Medical or surgical procedure (e.g. 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

Definition of Unsolicited and Solicited AE

- An unsolicited AE is an AE that was not solicited which is either recorded using a participant diary or is communicated by a participant/legally authorized representative who has signed the informed consent. Unsolicited AEs include serious and nonserious AEs.
- Potential unsolicited AEs may be medically attended (i.e. 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.
- Unsolicited AEs that are not medically attended nor perceived as a concern by the participant/legally authorized representative will be collected during an interview with the participant/legally authorized representative and by review of available medical records at the next visit.
- 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 their diary.

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 a 24-hour 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 (e.g. 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 (e.g. 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.
- 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

Any SAE must be reported by the investigator starting from the day of the first dose of study intervention (Day 1), whether or not the SAE is considered related to the study intervention. A copy of SAE report must be forwarded to the safety specialist designated by the Sponsor within 24 hours.

The Sponsor and/or designee will promptly notify all relevant investigators and the regulatory authorities of findings that could adversely affect the safety of participants, impact the conduct of the study or alter the IEC/IRB approval/favorable opinion of the study. In addition, the designee, on behalf of the Sponsor, will expedite the reporting to all concerned investigators, to the IECs/IRBs, where required, and to the regulatory authorities of all adverse reactions that are both serious and unexpected.

10.4. Appendix 4: Adverse Events of Special Interest

Each participant will be assessed for these autoimmune, hypersensitivity, and inflammatory diseases 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* • Acute disseminated encephalomyelitis (ADEM)*
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 considered potentially applicable to COVID-19 vaccines based on known association with vaccination in general, as reported in D2. 3 Priority list of adverse events of special interest: COVID-19

(SPEAC 2020, available at https://brightoncollaboration.us/wp-content/uploads/2020/06/SPEAC_D2.3_V2.0_COVID-19_20200525_public.pdf).

Source: Hyer R, McGuire DK, Xing B, Jackson S, Janssen R. Safety of a two-dose investigational hepatitis B vaccine, HBsAg-1018, using a toll-like receptor 9 agonist adjuvant in adults. Vaccine. 2018 May 3;36(19):2604-2611. doi: 10.1016/j.vaccine.2018.03.067.

10.5. Appendix 5: Vaccine-associated Enhanced Diseases

Each participant will be assessed for these potential VAED relevant to COVID-19 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
Immunologic	• Enhanced disease following immunization • Multisystem inflammatory syndrome in children
Respiratory	• Acute respiratory distress syndrome (ARDS)

Cardiac	• Acute cardiac injury including:
	  ○ Microangiopathy
	  ○ Heart failure and cardiogenic shock
	  ○ Stress cardiomyopathy
	  ○ Coronary artery disease
	  ○ Arrhythmia
	  ○ Myocarditis, pericarditis

Hematologic	• Coagulation disorder
	  ○ Deep vein thrombosis
	  ○ Pulmonary embolus
	  ○ Cerebrovascular stroke
	  ○ Limb ischemia
	  ○ Hemorrhagic disease

Renal	• Acute kidney injury
Gastrointestinal	• Liver injury
Neurologic	• Guillain Barré Syndrome • Anosmia, ageusia • Meningoencephalitis
Dermatologic	• Chilblain-like lesions • Single organ cutaneous vasculitis • Erythema multiforme

Source: Safety Platform for Emergency Vaccines (SPEAC). D2.3 Priority list of adverse events of special interest: COVID-19. Work Package: WP2 Standards and Tools. V2.0. 25 May 2020. Available at https://brightoncollaboration.us/wp-content/uploads/2020/06/SPEAC_D2.3_V2.0_COVID-19_20200525_public.pdf.

10.6. Appendix 6: Country-specific Requirements

10.6.1. Case Definition of COVID-19

The following extract shows the case definition of COVID-19 by (Taiwan Centers for Disease Control, Taiwan CDC), dated 16 April 2020 (Taiwan CDC 2020). Taiwan CDC will continue to update the case definition of COVID-19, and the latest version will be implemented into this study once available.

1. Clinical Presentation Criteria

One or more of the following:

(1) Fever (≥ 38℃) or symptoms of acute respiratory tract infection.
(2) Abnormal sense of smell (anosmia), abnormal sense of taste (dysgeusia), or diarrhea of unknown etiology.
(3) Community-acquired pneumonia (CAP) highly suspected to be COVID-19 by doctors.

2. Laboratory Diagnosis Criteria

One or more of the following:

(1) Pathogen (SARS-CoV-2) isolated and identified from a clinical specimen (nasopharyngeal swab, throat swab, expectorated sputum, or lower respiratory tract aspirates).
(2) Positive molecular biological testing for viral (SARS-CoV-2) RNA from a clinical specimen (nasopharyngeal swab, throat swab, expectorated sputum, or lower respiratory tract aspirates).

3. Epidemiological Criteria

One or more of the following within 14 days prior to symptom onset:

(1) History of traveling or living abroad, or contact with symptomatic (fever or other respiratory tract infection symptoms) individuals returning from abroad.
(2) History of close contact with symptomatic suspected or confirmed case(s), including caring for or interacting with these individuals, or direct contact with body fluid or respiratory secretions without adequate personal protective equipment (PPE).
(3) History of cluster related to confirmed cases.

4. Reporting Requirements for COVID-19

Any cases with one or more of the following conditions should be reported to the Taiwan Centers for Disease Control (Taiwan CDC):

(1) Meet clinical presentation criteria (1) AND one or more epidemiological criteria.
(2) Meet clinical presentation criteria (2) AND any of epidemiological criteria (1) or (2).
(3) Meet clinical presentation criteria (3).
(4) Meet laboratory diagnosis criteria.

5. Case definitions

(1) Suspected case: meet clinical presentation criteria but not laboratory proven, plus history of close contact with symptomatic confirmed case(s) within 14 days prior to symptom onset.

(2) Confirmed case: meet laboratory diagnosis criteria, regardless of clinical signs and symptoms.

10.6.2. Case Definition of Severe COVID-19

The US FDA recommends (FDA COVID-19 Vaccine 2020) that severe COVID-19 be defined as virologically confirmed SARS-CoV-2 infection with any of the following:

- Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥ 30 per minute, heart rate ≥ 125 per minute, $SpO_2 \leq 93\%$ on room air at sea level or PaO_2/FiO_2 < 300 mm Hg)
- Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation [ECMO])
- Evidence of shock (systolic blood pressure < 90 mm Hg, diastolic blood pressure < 60 mm Hg, or requiring vasopressors)
- Significant acute renal, hepatic, or neurologic dysfunction
- Admission to an intensive care unit (ICU)
- Death

10.7. Appendix 7: Detection of Vaccine-associated Enhanced Disease

For those adverse events which meet the event terms listed in VAED (Section 10.5, Appendix 5: Vaccine-associated Enhanced Diseases), the investigator shall proactively collect the result of pathogen (SARS-CoV-2) isolation or molecular biological testing for viral (SARS-CoV-2) RNA in his/her best capacity.

For those adverse events which meet the criteria of SAE, the investigator shall take VAED into consideration simultaneously upon reporting SAE (by selecting the checkbox of the VAED item shown in SAE report form as below table), and proactively seek to exclude or include VAED by negative or positive pathogen (SARS-CoV-2) isolation/ molecular biological testing for viral (SARS-CoV-2) RNA, respectively.

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

1. GENERAL INFORMATION		
PROTOCOL No.: CT-COV-21	COUNTRY:	SITE ID:
☐ SAE	☐ AESI, ……	☐VAED, ……

10.8. Appendix 8: Abbreviations

ACE2	Angiotensin-converting enzyme 2
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
CRF	Case report form
CRO	Contract research organization
CV	Coefficient of variation
ECG	Electrocardiography
ECMO	Extracorporeal Membrane Oxygenation
eCRF	Electronic Case Report Forms
EOS	End of study
ET	Early termination
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GMT	Geometric mean titers
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HbA1c	Hemoglobin A1c
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	Intensive care unit
IDMC	Independent Data Monitoring Committee
IEC	Independent ethics committees
IM	Intramuscular
IRB	Institutional Review Board
IV	Intravenous
IWRS	Interactive Web Response System
LoD	Lower limit of detection
MedDRA	Medical Dictionary for Regulatory Activities
MERS-CoV	Middle East respiratory syndrome coronavirus
ODN	Oligodeoxynucleotide
pDCs	Plasmacytoid dendritic cells
PIC/S	Pharmaceutical Inspection Co-operation Scheme
PPE	Personal Protective Equipment
PPI	Per protocol Immunogenicity

PPS	Per protocol Set
PT	Preferred term
RBD	Receptor binding domain
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
SoA	Schedule of activities
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected unexpected serious adverse reactions
TNF	Tumor necrosis factor
TOST	Two one-sided tests
US	United States
VAED	Vaccine-associated enhanced disease

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