Supplementary Appendix

Song et al. Immunogenicity and safety of SARS-CoV-2 recombinant protein nanoparticle vaccine GBP510 adjuvanted with AS03: interim results of a randomised, active-controlled, observer-blinded, phase 3 trial.

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I. Supplementary Tables

Table S1. Adverse events of special interests (AESIs) relevant to COVID-19

AESI included because they are seen with COVID-19 Disease [3,4]
Acute respiratory distress syndrome
Multisystem inflammatory syndrome (children & adults)
Acute cardiovascular injury (includes: myocarditis/pericarditis, microangiopathy, heart failure, stress cardiomyopathy, coronary artery disease arrhythmia)
Coagulation disorder (includes: thrombotic disorders, bleeding disorders)
Anosmia, ageusia
Chilblain – like lesions
Erythema multiforme
Single Organ Cutaneous Vasculitis
Acute kidney injury
Acute liver injury
Acute pancreatitis
Rhabdomyolysis
Subacute thyroiditis
AESI included because they have a proven or theoretical association with immunization in general
Anaphylaxis [1,2]
Thrombocytopenia [1,2,3,4]
Generalized convulsion [1,2]
Acute disseminated encephalomyelitis [4]
Guillain Barré Syndrome [3,4]
AESI included because they have a proven or theoretical association with specific vaccine platform(s)
Acute aseptic arthritis [r-VSV]
Aseptic meningitis [Live vaccines]
Encephalitis / Encephalomyelitis [Live vaccines]
Idiopathic Peripheral Facial Nerve Palsy [Intranasal E. coli Heat Labile Toxin Adjuvanted Vaccine]
Vaccine associated enhanced disease [1(Formalin inactivated measles/RSV; HIV), 2(Chimeric YF Dengue), 5 (SARS/MERS-CoVs)]
Thrombosis with thrombocytopenia syndrome [Recombinant adenoviral vector vaccines]

[1] Proven association with immunization encompassing several different vaccines

[2] Proven association with vaccine that could theoretically be true for novel COVID-19 vaccines

[3] Theoretical concern based on wild type disease immunopathogenesis

[4] Theoretical concern related to viral replication during wild type disease

[5] Theoretical concern because it has been demonstrated in an animal model with ≥1 vaccine platform

Ref) Brighton Collaboration: Safety Platform for Emergency Vaccines (SPEAC). (2020). Priority List of Adverse Events of Special Interest: COVID-19. https://brightoncollaboration.us/prioritylist-aesi-covid

Table S2. Potential Immune-Mediated Diseases (PIMDs) included as adverse events of special interests

Medical Concept	Additional Notes
Blood disorders and coagulopathies	
Antiphospholipid syndrome	
Autoimmune anemia aplastic	
Autoimmune anemia hemolytic	• Includes warm antibody hemolytic anemia and cold antibody hemolytic anemia
Autoimmune lymphoproliferative syndrome (ALPS)	
Autoimmune neutropenia	
Autoimmune pancytopenia	
Autoimmune thrombocytopenia	• Frequently used related terms include: "autoimmune thrombocytopenic purpura", "idiopathic thrombocytopenic purpura (ITP)","idiopathic immune thrombocytopenia", "primary immune thrombocytopenia".
Evans syndrome	
Pernicious anemia	
Thrombosis with thrombocytopenia syndrome (TTS)	
Thrombotic thrombocytopenic purpura	• Also known as "Moschcowitz-syndrome" or "microangiopathic hemolytic anemia"
Cardio-pulmonary inflammatory disorders	
Idiopathic Myocarditis/Pericarditis	Including but not limited to: • Autoimmune / Immune-mediated myocarditis • Autoimmune / Immune-mediated pericarditis • Giant cell myocarditis
Idiopathic fibrosis pulmonary	Including but not limited to: • Idiopathic interstitial pneumonia (frequently used related terms include "Interstitial lung disease", "Pulmonary fibrosis", "Immune-mediated pneumonitis") • Pleuroparenchymal fibroelastosis (PPFE)
Pulmonary alveolar proteinosis (PAP)	• Frequently used related terms include: "pulmonary alveolar lipoproteinosis", "phospholipidosis"
Endocrine disorders	
Addison's disease	
Autoimmune /Immune- mediated thyroiditis	Including but not limited to: • Hashimoto thyroiditis (autoimmune hypothyroidism, lymphocytic thyroiditis) • Atrophic thyroiditis • Silent thyroiditis • Thyrotoxicosis
Autoimmune diseases of the testis and ovary	• Includes autoimmune oophoritis, autoimmune ovarian failure and autoimmune orchitis
Autoimmune hyperlipidemia	
Autoimmune hypophysitis	

Diabetes mellitus type I	
Grave's or Basedow's disease	• Includes Marine Lenhart syndrome and Graves' ophthalmopathy, also known as thyroid eye disease (TED) or endocrine ophthalmopathy
Insulin autoimmune syndrome	
Polyglandular autoimmune syndrome	• Includes Polyglandular autoimmune syndrome type I, II and III
Eye disorders	
Ocular Autoimmune / Immune-mediated disorders	Including but not limited to: • Acute macular neuroretinopathy (also known as acute macular outer retinopathy) • Autoimmune / Immune-mediated retinopathy • Autoimmune / Immune-mediated uveitis, including idiopathic uveitis and sympathetic ophthalmia • Cogan's syndrome: an oculo-audiovestibular disease • Ocular pemphigoid • Ulcerative keratitis • Vogt-Koyanagi-Harada disease
Gastrointestinal disorders	
Autoimmune/Immune-mediated pancreatitis	
Celiac disease	
Inflammatory bowel disease	Including but not limited to: • Crohn's disease • Microscopic colitis • Terminal ileitis • Ulcerative colitis • Ulcerative proctitis
Hepatobiliary disorders	
Autoimmune cholangitis	
Autoimmune hepatitis	
Primary biliary cirrhosis	
Primary sclerosing cholangitis	
Musculoskeletal and connective tissue disorders	
Gout	• Includes gouty arthritis
Idiopathic inflammatory myopathies	Including but not limited to: • Dermatomyositis • Inclusion body myositis • Immune-mediated necrotizing myopathy • Polymyositis
Mixed connective tissue disorder	
Polymyalgia rheumatica (PMR)	

Psoriatic arthritis (PsA)	
Relapsing polychondritis	
Rheumatoid arthritis	Including but not limited to: ● Rheumatoid arthritis associated conditions ● Juvenile idiopathic arthritis ● Palindromic rheumatism ● Still's disease ● Felty's syndrome
Sjögren's syndrome	
Spondyloarthritis	Including but not limited to: ● Ankylosing spondylitis ● Juvenile spondyloarthritis ● Keratoderma blenorrhagica ● Psoriatic spondylitis ● Reactive Arthritis (Reiter's Syndrome) ● Undifferentiated spondyloarthritis
Systemic Lupus Erythematosus	● Includes Lupus associated conditions (e.g. Cutaneous lupus erythematosus, Lupus nephritis, etc.) or complications such as shrinking lung syndrome (SLS)
Systemic Scleroderma (Systemic Sclerosis)	● Includes Reynolds syndrome (RS), systemic sclerosis with diffuse scleroderma and systemic sclerosis with limited scleroderma (also known as CREST syndrome)
Neuroinflammatory/neuromuscular disorders	
Acute disseminated encephalomyelitis (ADEM) and other inflammatory-demyelinating variants	Includes the following: ● Acute necrotising myelitis ● Bickerstaff's brainstem encephalitis ● Disseminated necrotizing leukoencephalopathy (also known as Weston-Hurst syndrome, acute hemorrhagic leukoencephalitis, or acute necrotizing hemorrhagic encephalomyelitis) ● Myelin oligodendrocyte glycoprotein antibody-associated disease ● Neuromyelitis optica (also known as Devic's disease) ● Noninfective encephalitis / encephalomyelitis / myelitis ● Postimmunization encephalomyelitis
Guillain-Barré syndrome (GBS)	● Includes variants such as Miller Fisher syndrome and the acute motor and sensory axonal neuropathy (AMSAN)
Idiopathic cranial nerve palsies/paresis and inflammations (neuritis)	Including but not limited to: ● Cranial nerve neuritis (e.g. Optic neuritis) ● Idiopathic nerve palsies/paresis (e.g. Bell's palsy) ● Melkersson-Rosenthal syndrome ● Multiple cranial nerve palsies/paresis

Multiple Sclerosis (MS)	Includes the following: • Clinically isolated syndrome (CIS) • Malignant MS (the Marburg type of MS) • Primary-progressive MS (PPMS) • Radiologically isolated syndrome (RIS) • Relapsing-remitting MS (RRMS) • Secondary-progressive MS (SPMS) • Uhthoff's phenomenon
Myasthenia gravis	• Includes ocular myasthenia and Lambert-Eaton myasthenic syndrome
Narcolepsy	• Includes narcolepsy with or without presence of unambiguous cataplexy
Peripheral inflammatory demyelinating neuropathies and plexopathies	Including but not limited to: • Acute Brachial Radiculitis (also known as Parsonage-Turner Syndrome or neuralgic amyotrophy) • Antibody-mediated demyelinating neuropathy • Chronic idiopathic axonal polyneuropathy (CIAP) • Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP), including atypical CIDP variants (e.g. multifocal acquired demyelinating sensory and motor neuropathy also known as Lewis-Sumner syndrome) • Multifocal motor neuropathy (MMN)
Transverse myelitis ©	• Includes acute partial transverse myelitis (APTM) and acute complete transverse myelitis (ACTM)
Renal disorders	
Autoimmune / Immune- mediated glomerulonephritis	Including but not limited to: • IgA nephropathy • IgM nephropathy • C1q nephropathy • Fibrillary glomerulonephritis • Glomerulonephritis rapidly progressive • Membranoproliferative glomerulonephritis • Membranous glomerulonephritis • Mesangioproliferative glomerulonephritis • Tubulointerstitial nephritis and uveitis syndrome
Skin and subcutaneous tissue disorders	
Alopecia areata	
Autoimmune / Immune- mediated blistering dermatoses	Including but not limited to: • Bullous Dermatitis • Bullous Pemphigoid • Dermatitis herpetiformis • Epidermolysis bullosa acquisita (EBA) • Linear IgA-mediated bullous dermatosis (LABD), also known as Linear IgA disease • Pemphigus

Erythema multiforme	
Erythema nodosum	
Reactive granulomatous dermatitis	Including but not limited to • Interstitial granulomatous dermatitis • Palisaded neutrophilic granulomatous dermatitis
Lichen planus	• Includes liquen planopilaris
Localised Scleroderma (Morphoea)	• Includes Eosinophilic fasciitis (also called Shulman syndrome)
Psoriasis	
Pyoderma gangrenosum	
Stevens-Johnson Syndrome (SJS)	Including but not limited to: • Toxic Epidermal Necrolysis (TEN) • SJS-TEN overlap
Sweet's syndrome	• Includes Acute febrile neutrophilic dermatosis
Vitiligo	
Vasculitis	
Large vessels vasculitis	Including but not limited to: • Arteritic anterior ischemic optic neuropathy (AAION or arteritic AION) • Giant cell arteritis (also called temporal arteritis) • Taka'asu's arteritis
Medium sized and/or small vessels vasculitis	Including but not limited to: • Anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified) • Be'cet's syndrome • Buerger's disease (thromboangiitis obliterans) • Churg–Strauss syndrome (allergic granulomatous angiitis) • Erythema induratum (also known as nodular vasculitis) • Henoch-Schonlein purpura (also known as IgA vasculitis) • Microscopic polyangiitis • Necrotizing vasculitis • Polyarteritis nodosa • Single organ cutaneous vasculitis, including leukocytoclastic vasculitis, hypersensitivity vasculitis and acute hemorrhagic edema of infancy (AHEI) • Weg'ner's granulomatosis
Other (including multisystemic)	
Anti-synthetase syndrome	
Capillary leak syndrome	• Frequently used related terms include : "systemic capillary leak syndrome (SCLS)" or "Clar'son's Syndrome"
Goodpasture syndrome	• Frequently used related terms include : "pulmonary renal syndrome" and "anti-Glomerular Basement Membrane disease (anti-GBM disease)"

Immune-mediated enhancement of disease	• Includes vaccine associated enhanced disease (VAED and VAERD). Frequently used related terms include “vaccine- mediated enhanced disease (VMED)”, “enhanced respiratory disease (ERD)”, “vaccine-induced enhancement of
	infection”, “disease enhancement”, “immune enhancement”, and “antibody-dependent enhancement (ADE)
Immunoglobulin G4 related disease	
Langer’ans' cell histiocytosis	
Multisystem inflammatory syndromes	Including but not limited to: • Kawasaki’s disease • Multisystem inflammatory syndrome in adults (MIS-A) • Multisystem inflammatory syndrome in children (MIS-C)
Overlap syndrome	
Raynaud’s phenomenon	
Sarcoidosis	• Includes Loefgren syndrome
S’sac's syndrome	

Table S3. Study Disposition Screened Set [6M Follow up]

	GBP510	ChAdOx1-S	Total
Screening			4913
Screening Failure			877
Primary Reason for Screening Failure[1], n (%)			
Subject did not fulfil all eligibility criteria			401(8·16)
Withdraw consent			17(0·35)
Subject's conditions or other reasons for which conduct of required examination is not feasible			2(0·04)
Under PI decision			0
Others			457(9·30)
Randomized Set[2, 3], n (%)	3039	997	4036
1st vaccination	3030(99·70)	995(99·80)	4025(99·73)
2nd vaccination	2900(95·43)	958(96·09)	3858(95·59)
Not vaccinated	9(0·30)	2(0·20)	11(0·27)
Status[2, 3], n (%)			
Completion	2750(90·49)	879(88·16)	3629(89·92)
Discontinuation	262(8·62)	108(10·83)	370(9·17)
Stage 2	27(0·89)	10(1·00)	37(0·92)

PI = principal investigator, AEs = adverse events, SAEs = serious adverse events.

Note: 1) Denominator of percentage is the number of screened participants.

2) Denominator of percentage is the number of randomized participants.

3) The number of participants were displayed according to planned treatment group. One participant was administered incorrect IP inconsistent (ChAdOx1-S) with randomization assignment (GBP510).

Table S4. Major Protocol Deviations Intention-to-Treat Set [6M Follow up]

	GBP510 (N=3039)	ChAdOx1-S (N=997)	Total (N=4036)
Participants with Major Protocol Deviation	659(21·68) [1205]	249(24·97) [463]	908(22·50) [1668]
Visit Window Deviation	237(7·80) [251]	78(7·82) [81]	315(7·80) [332]
Efficacy Variables Check	187(6·15) [308]	76(7·62) [134]	263(6·52) [442]
Safety Variables Check	180(5·92) [248]	78(7·82) [100]	258(6·39) [348]
Other	181(5·96) [191]	65(6·52) [68]	246(6·10) [259]
IP Administration Deviation	105(3·46) [120]	34(3·41) [42]	139(3·44) [162]
Prohibited Medications	70(2·30) [70]	29(2·91) [29]	99(2·45) [99]
Exclusion Criteria Deviation	8(0·26) [8]	4(0·40) [4]	12(0·30) [12]
Eligibility	9(0·30) [9]	2(0·20) [2]	11(0·27) [11]
Test Window Deviation	0	1(0·10) [3]	1(0·02) [3]

Note: Protocol deviations are displayed as 'number of individuals (percentage of individuals) [number of event]'.
Data Source: Listing 16·2·3-1.

Table S5. Analysis Sets Intention-to-Treat Set [6M Follow up]

	GBP510 (N=3039)	ChAdOx1-S (N=997)	Total (N=4036)
Safety Set[3], n(%)	3029(99·70)	996(99·80)	4025(99·73)
Reason for Exclusion from Safety Set[1], n (%)			
Not treated	9(100·00)	2(100·00)	11(100·00)
Immunogenicity Sets[2], n (%)			
Full Analysis Set	1259(41·55)	628(63·12)	1887(46·88)
PPS 1 for Primary stage (Visit 1 to 6)	877(69·66)	441(70·22)	1318(69·85)
PPS 2 for Extension stage (Visit 7 to 8)	604(68·87)	310(70·29)	914(69·35)
Reason for Exclusion from FAS[1, 2], n (%)			
No valid both pre- and at least one post-vaccination immunogenicity assessment results	40(2·26)	21(5·72)	61(2·85)
Cohort 2	1731(97·74)	346(94·28)	2077(97·15)
Reason for Exclusion from PPS 1 for Primary stage (Visit 1 to 6)[1, 2], n (%)			
Participant did not meet all inclusion criteria or met at least one of the exclusion criteria	1(0·26)	1(0·53)	2(0·35)
Participant did not complete the vaccination schedule	3(0·79)	0	3(0·53)
Preparation and / or administration of study intervention was not done as per-protocol	13(3·40)	9(4·81)	22(3·87)
Any of the blood samples were not drawn, or not drawn in the proper time window until Visit 6 (Day 14+3 after Visit 4)	94(24·61)	47(25·13)	141(24·78)
Participant received a protocol-prohibited medication or vaccine from Visit 2 (Day 0) to Visit 6 (Day 14+3 after Visit 4)	1(0·26)	0	1(0·18)
Participant with FRNT value at baseline is above LLOQ	113(29·58)	54(28·88)	167(29·35)
With positive for SARS-CoV-2 Ab N-protein test	141(36·91)	66(35·29)	207(36·38)
No result for Immunoassay for SARS-CoV-2 at V6	1(0·26)	0	1(0·18)
Participant with confirmed/suspected COVID-19	12(3·14)	8(4·28)	20(3·51)
Withdrawal before Visit 6	3(0·79)	2(1·07)	5(0·88)
Reason for Exclusion from PPS 2 for Extension stage (Visit 7 to 8)[1, 2], n (%)			
Any of the blood samples were not drawn, or not drawn in the proper time window until Visit 8 (Day 168±14 after Visit 4)	140(51·28)	73(55·73)	213(52·72)

	GBP510 (N=3039)	ChAdOx1-S (N=997)	Total (N=4036)
Participant received a protocol-prohibited medication or vaccine from Visit 2 (Day 0) to Visit 8 (Day 168±14 after Visit 4)	25(9·16)	14(10·69)	39(9·65)
Participant with confirmed/suspected COVID-19 until Visit 8 (Day 168±14 after Visit 4)	85(31·14)	36(27·48)	121(29·95)
Participant joined Stage 2 before Visit 8	23(8·42)	8(6·11)	31(7·67)

FAS = full analysis set, PPS 1 = per-protocol set 1, PPS 2 = per-protocol set 2.
Note: Denominator of percentage is the number of participants in each group.
1) Denominator of percentage is the number of excluding from analysis set.
2) The number of participants were displayed according to planned treatment group.
3) The number of participants for safety set were displayed according to actual treatment group.
One participant was administered incorrect IP inconsistent (ChAdOx1-S) with randomization assignment (GBP510).
Data Source: Listing 16·2·4-1.

Table S6. Demographics and baseline characteristics (Per-Protocol Set)

	GBP510 (N=877)	ChAdOx1-S (N=441)	Total (N=1,318)
Age at randomization (years)			
n	877	441	1,318
Mean (SD)	41·6(12·4)	42·3(12·3)	41·8(12·4)
Median	42·00	42·00	42·00
Min, Max	18·00, 79·00	18·00, 76·00	18·00, 79·00
Age group at randomization, n (%)			
18~64 years	834(95·10)	417(94·56)	1,251(94·92)
≥ 65 years	43(4·90)	24(5·44)	67(5·08)
Sex, n (%)			
Male	530(60·43)	251(56·92)	781(59·26)
Female	347(39·57)	190(43·08)	537(40·74)
Race, n (%)			
Asian	832(94·87)	420(95·24)	1,252(94·99)
Korean	303(34·55)	154(34·92)	457(34·67)
Southeast Asian	529(60·32)	266(60·32)	795(60·32)
Other	0(0·00)	0(0·00)	0(0·00)
Caucasian	45(5·13)	21(4·76)	66(5·01)
Black	0(0·00)	0(0·00)	0(0·00)
Hispanic	0(0·00)	0(0·00)	0(0·00)
Other	0(0·00)	0(0·00)	0(0·00)
BMI (kg/m^2)			
n	877	441	1,318
Mean (SD)	24·0(4·3)	24·3(3·9)	24·1(4·1)
Median	23·50	24·00	23·70
Min, Max	13·20, 46·40	15·40, 36·70	13·20, 46·40

SD = standard deviation, Min = minimum, Max = maximum, BMI = body mass index.
BMI (kg/m^2) = weight (kg)/[height (cm)×0·01]^2.
Note: Denominator of percentage is the number of participants in each group.

Table S7. Immunogenicity Assessment by Live Virus Neutralization Assays by FRNT ND50 (Extension Per-Protocol Set) [6M Follow up]

Unit Converted to IU/mL	GBP510 (N=604)	ChAdOx1-S (N=310)
Baseline		
n	604	310
GMT(SD)	8·17(1·08)	8·12(1·05)
95% Confidence Interval	[8·12, 8·21]	[8·07, 8·16]
Ratio of GMTs (GBP510 / ChAdOx1-S)(SD)	1·01(NA)	
95% Confidence Interval	[1·00, 1·01]	
P-value [1]	0·15	
Visit 4 (4 weeks after 1st vaccination)		
n	132	69
GMT(SD)	11·03(2·24)	51·07(3·54)
95% Confidence Interval	[9·60, 12·68]	[37·71, 69·18]
Ratio of GMTs (GBP510 / ChAdOx1-S)(SD)	0·22(NA)	
95% Confidence Interval	[0·15, 0·30]	
P-value [1]	<0·0001	
GMFR(SD)	1·36(2·24)	6·28(3·48)
95% Confidence Interval	[1·18, 1·56]	[4·66, 8·47]
Adjusted GMT(SE)†	11·54(1·18)	51·05(1·20)
95% Confidence Interval	[8·26, 16·12]	[35·87, 72·66]
Ratio of GMTs (GBP510 / ChAdOx1-S)(SE)	0·23(1·16)	
95% Confidence Interval	[0·17, 0·30]	
P-value [2]	<0·0001	
Participants with ≥ 4-fold rise, n(%)	6(4·55)	44(63·77)
95% Confidence Interval	[1·69, 9·63]	[51·31, 75·01]
Difference in Proportions of the Participant with ≥ 4-fold rise	-59·22	
95% Confidence Interval	[-70·57, -46·41]	
P-value [3]	<0·0001 (c)	
Visit 6 (2 weeks after 2nd vaccination)		
n	604	310
GMT(SD)	305·36(2·62)	107·47(2·78)
95% Confidence Interval	[282·78, 329·74]	[95·87, 120·47]
Ratio of GMTs (GBP510 / ChAdOx1-S)(SD)	2·84(2·67)	
95% Confidence Interval	[2·48, 3·25]	
P-value [1]	<0·0001	
GMFR(SD)	37·39(2·62)	13·24(2·78)
95% Confidence Interval	[34·63, 40·38]	[11·81, 14·84]
Adjusted GMT(SE)†	289·20(1·08)	102·23(1·09)
95% Confidence Interval	[249·08, 335·78]	[86·57, 120·73]
Ratio of GMTs (GBP510 / ChAdOx1-S)(SE)	2·83(1·07)	
95% Confidence Interval	[2·47, 3·24]	
P-value [2]	<0·0001	

Unit Converted to IU/mL	GBP510 (N=604)	ChAdOx1-S (N=310)
Participants with ≥ 4-fold rise, n(%)	590(97·68)	272(87·74)
95% Confidence Interval	[96·14, 98·73]	[83·56, 91·18]
Difference in Proportions of the Participant with ≥ 4-fold rise	9·94	
95% Confidence Interval	[6·31, 14·24]	
P-value [3]	<0·0001 (c)	
Visit 8 (6 months after 2nd vaccination)		
n	604	310
GMT(SD)	189·94(4·20)	113·16(6·71)
95% Confidence Interval	[169·36, 213·03]	[91·48, 139·98]
Ratio of GMTs (GBP510 / ChAdOx1-S)(SD)	1·68(NA)	
95% Confidence Interval	[1·32, 2·14]	
P-value [1]	<0·0001	
GMFR(SD)	23·26(4·20)	13·94(6·72)
95% Confidence Interval	[20·74, 26·08]	[11·26, 17·24]
Adjusted GMT(SE)†	217·99(1·13)	130·00(1·15)
95% Confidence Interval	[170·65, 278·45]	[99·00, 170·71]
Ratio of GMTs (GBP510 / ChAdOx1-S)(SE)	1·68(1·12)	
95% Confidence Interval	[1·34, 2·09]	
P-value [2]	<0·0001	
Participants with ≥ 4-fold rise, n(%)	541(89·57)	205(66·13)
95% Confidence Interval	[86·85, 91·89]	[60·56, 71·38]
Difference in Proportions of the Participant with ≥ 4-fold rise	23·44	
95% Confidence Interval	[17·62, 29·42]	
P-value [3]	<0·0001 (c)	

GMT = geometric mean titre, SD = standard deviation, SE = standard error, GMFR = geometric mean fold rise, ANCOVA = analysis of covariance, NA = not applicable.
Assay unit: IU/mL
[1] Testing for difference between treatment groups (two sample t-test).
[2] † ANCOVA model with treatment group, age group (18~64, ≥65) as factors, and baseline antibody level as covariate.
[3] Testing for difference between treatment groups (chi-square test (c) or Fisher's exact test (f)).
GMT = anti-logarithm [mean of logarithm (titre at visit n)], GMFR = anti-logarithm [mean of logarithm (titre at visit n/titre at visit 2)].
When two samples had unequal variance, the standard deviation for the ratio of GMT is presented 'NA'.
The test results are collected for randomly selected participants (about 20% of all participants) at Visit 4.
The 95% CI for GMT and GMFR are calculated using Wald method with t-distribution.
The 95% CI of percentage of participants ≥ 4-fold rises is calculated based on Clopper-Pearson method.
The 95% CI of the difference between groups is calculated based on Chan and Zhang method.
If ANCOVA model has infinite likelihood, ANCOVA under the assumption of homoscedasticity is used.
Data Source: Listing 16·2·8-1.

Table S8. Immunogenicity Assessment of SARS-CoV-2 RBD-binding IgG antibody by ELISA (Extension Per-Protocol Set) [6M Follow up]

Unit: BAU/mL	GBP510 (N=604)	ChAdOx1-S (N=310)
Baseline		
n	604	310
GMT(SD)	11·03(1·78)	10·87(1·70)
95% Confidence Interval	[10·53, 11·55]	[10·24, 11·53]
Ratio of GMTs (GBP510 / ChAdOx1-S)(SD)	1·01(1·75)	
95% Confidence Interval	[0·94, 1·10]	
P-value [1]	0·71	
Visit 4 (4 weeks after 1st vaccination)		
n	604	310
GMT(SD)	174·19(2·35)	122·70(2·40)
95% Confidence Interval	[162·70, 186·50]	[111·28, 135·28]
Ratio of GMTs (GBP510 / ChAdOx1-S)(SD)	1·42(2·37)	
95% Confidence Interval	[1·26, 1·60]	
P-value [1]	<0·0001	
GMFR(SD)	15·79(2·62)	11·29(2·72)
95% Confidence Interval	[14·62, 17·05]	[10·09, 12·62]
Adjusted GMT(SE)†	131·74(1·07)	93·95(1·08)
95% Confidence Interval	[115·94, 149·69]	[81·49, 108·32]
Ratio of GMTs (GBP510 / ChAdOx1-S)(SE)	1·40(1·06)	
95% Confidence Interval	[1·25, 1·57]	
P-value [2]	<0·0001	
Participants with ≥ 4-fold rise, n(%)	557(92·22)	264(85·16)
95% Confidence Interval	[89·79, 94·23]	[80·71, 88·93]
Difference in Proportions of the Participant with ≥ 4-fold rise	7·06	
95% Confidence Interval	[2·56, 11·55]	
P-value [3]	0·0008 (c)	
Visit 6 (2 weeks after 2nd vaccination)		
n	604	310
GMT(SD)	3218·30(2·12)	250·54(2·23)
95% Confidence Interval	[3030·73, 3417·48]	[229·02, 274·08]
Ratio of GMTs (GBP510 / ChAdOx1-S)(SD)	12·85(2·16)	
95% Confidence Interval	[11·56, 14·28]	
P-value [1]	<0·0001	
GMFR(SD)	291·76(2·63)	23·05(2·48)
95% Confidence Interval	[270·08, 315·17]	[20·83, 25·51]
Adjusted GMT(SE)†	2806·28(1·06)	214·45(1·07)
95% Confidence Interval	[2502·76, 3146·60]	[188·77, 243·61]
Ratio of GMTs (GBP510 / ChAdOx1-S)(SE)	13·09(1·05)	
95% Confidence Interval	[11·80, 14·51]	

Unit: BAU/mL	GBP510 (N=604)	ChAdOx1-S (N=310)
P-value [2]	<0·0001	
Participants with ≥ 4-fold rise, n(%)	601(99·50)	300(96·77)
95% Confidence Interval	[98·56, 99·90]	[94·15, 98·44]
Difference in Proportions of the Participant with ≥ 4-fold rise	2·73	
95% Confidence Interval	[0·68, 4·77]	
P-value [3]	0·0018 (f)	
Ratio of GMTs (GBP510 / ChAdOx1-S)(SD)	12·30(NA)	
95% Confidence Interval	[11·09, 13·64]	
P-value [1]	<0·0001	
GMFR(SD)	219·20(2·37)	18·09(2·43)
95% Confidence Interval	[204·61, 234·83]	[16·38, 19·98]
Adjusted GMT(SE)†	2166·45(1·06)	174·24(1·06)
95% Confidence Interval	[1949·45, 2407·61]	[154·92, 195·97]
Ratio of GMTs (GBP510 / ChAdOx1-S)(SE)	12·43(1·05)	
95% Confidence Interval	[11·31, 13·67]	
P-value [2]	<0·0001	
Participants with ≥ 4-fold rise, n(%)	602(99·67)	296(95·48)
95% Confidence Interval	[98·81, 99·96]	[92·54, 97·51]
Difference in Proportions of the Participant with ≥ 4-fold rise	4·19	
95% Confidence Interval	[1·83, 6·54]	
P-value [3]	<0·0001 (c)	
Visit 8 (6 months after 2nd vaccination)		
n	604	310
GMT(SD)	630·48(2·32)	120·51(3·64)
95% Confidence Interval	[589·55, 674·24]	[104·30, 139·23]
Ratio of GMTs (GBP510 / ChAdOx1-S)(SD)	5·23(NA)	
95% Confidence Interval	[4·46, 6·13]	
P-value [1]	<0·0001	
GMFR(SD)	57·16(2·74)	11·09(4·00)
95% Confidence Interval	[52·73, 61·96]	[9·50, 12·95]
Adjusted GMT(SE)†	693·92(1·08)	132·37(1·09)
95% Confidence Interval	[594·72, 809·67]	[111·48, 157·17]
Ratio of GMTs (GBP510 / ChAdOx1-S)(SE)	5·24(1·07)	
95% Confidence Interval	[4·56, 6·03]	
P-value [2]	<0·0001	
Participants with ≥ 4-fold rise, n(%)	601(99·50)	222(71·61)
95% Confidence Interval	[98·56, 99·90]	[66·24, 76·57]
Difference in Proportions of the Participant with ≥ 4-fold rise	27·89	
95% Confidence Interval	[22·84, 32·94]	
P-value [3]	<0·0001 (c)	

Unit: BAU/mL	GBP510 (N=604)	ChAdOx1-S (N=310)

GMT = geometric mean titre, SD = standard deviation, SE = standard error, GMFR = geometric mean fold rise, ANCOVA = analysis of covariance, NA = not applicable.
Assay unit: BAU/mL
[1] Testing for difference between treatment groups (two sample t-test).
[2] † ANCOVA model with treatment group, age group (18~64, ≥65) as factors, and baseline antibody level as covariate.
[3] Testing for difference between treatment groups (chi-square test (c) or Fisher's exact test (f)).
GMT = anti-logarithm [mean of logarithm(titre at visit n)], GMFR = anti-logarithm[mean of logarithm(titre at visit n/titre at visit 2)].
When two samples had unequal variance, the standard deviation for the ratio of GMT is presented 'NA'.
The test results are collected for randomly selected participants (about 20% of all participants) at Visit 4.
The 95% CI for GMT and GMFR are calculated using Wald method with t-distribution.
The 95% CI of percentage of participants ≥ 4-fold rises is calculated based on Clopper-Pearson method.
The 95% CI of the difference in percentage of participants ≥ 4-fold rises between groups is calculated based on Wald method.
Data Source: Listing 16·2·8-1.

Table S9. Immunogenicity Assessment by Live Virus Neutralisation Assays (FRNT ND50) [Subgroup: Age Group: 18-64 years/≥ 65 years] up to 2 weeks after 2nd vaccination (Per-Protocol Set)

	18-64 years		≥ 65 years	
Unit Converted to IU/mL	**GBP510 (N=834)**	**ChAdOx1-S (N=417)**	**GBP510 (N=43)**	**ChAdOx1-S (N=24)**
Baseline				
n	834	417	43	24
GMT(SD)	8·17(1·08)	8·13(1·06)	8·29(1·13)	8·08(1·00)
95% Confidence Interval	[8·13, 8·22]	[8·09, 8·18]	[7·99, 8·60]	[8·08, 8·08]
Ratio of GMTs (GBP510 / ChAdOx1-S)(SD)	1·01(NA)		13(NA)	
95% Confidence Interval	[1·00, 1·01]		[0·99, 1·06]	
P-value [1]	0·17		0·16	
Visit 4 (4 weeks after 1st vaccination)				
n	187	88	8	8
GMT(SD)	11·49(2·28)	40·74(3·56)	8·08(1·00)	49·81(2·55)
95% Confidence Interval	[10·20, 12·94]	[31·14, 53·30]	[8·08, 8·08]	[22·78, 108·92]
Ratio of GMTs (GBP510 / ChAdOx1-S)(SD)	0·28(NA)		0·16(NA)	
95% Confidence Interval	[0·21, 0·38]		[0·07, 0·35]	
P-value [1]	<0·0001		0·0009	
GMFR(SD)	1·41(2·28)	5·02(3·51)	1·00(1·00)	6·17(2·55)
95% Confidence Interval	[1·26, 1·59]	[3·85, 6·54]	[1·00, 1·00]	[2·82, 13·48]
Adjusted GMT(SE)†	11·48(1·07)	40·79(1·11)	8·08(1·26)	49.81(1.26)
95% Confidence Interval	[9·97, 13·22]	[33·22, 50·10]	[4·89, 13·35]	[30.16, 82.27]
Ratio of GMTs (GBP510 / ChAdOx1-S)(SE)	0·28(1·13)		0·16(1·39)	
95% Confidence Interval	[0·22, 0·36]		[0·08, 0·33]	
P-value [2]	<0·0001		<0·0001	
Participants with ≥ 4-fold rise, n(%)	11(5·88)	49(55·68)	0(0·00)	5(62·50)
95% Confidence Interval	[2·97, 10·28]	[44·70, 66·27]	[0·00, 36·94]	[24·49, 91·48]
Difference in Proportions of the Participant with ≥ 4-fold rise	-49·80		-62·50	
95% Confidence Interval	[-60·85, -38·58]		[-91·48, -17·29]	
P-value [3]	<0·0001 (c)		0.03 (f)	
Visit 6 (2 weeks after 2nd vaccination)				
n	834	417	43	24
GMT(SD)	304·52(2·48)	103·01(2·72)	234·69(3·57)	89·29(3·56)
95% Confidence Interval	[286·29, 323·92]	[93·56, 113·40]	[158·63, 347·21]	[52·24, 152·62]
Ratio of GMTs (GBP510 / ChAdOx1-S)(SD)	2·96(NA)		2·63(3·57)	
95% Confidence Interval	[2·64, 3·31]		[1·38, 5·02]	
P-value [1]	<0·0001		0·004	
GMFR(SD)	37·26(2·48)	12·67(2·72)	28·31(3·65)	11·05(3·56)
95% Confidence Interval	[35·03, 39·63]	[11·51, 13·95]	[19·01, 42·16]	[6·47, 18·89]
Adjusted GMT(SE)†	304·31(1·03)	103·15(1·05)	235·83(1·21)	87·27(1·30)
95% Confidence Interval	[285·49, 324·37]	[94·24, 112·90]	[159·97, 347·66]	[51·71, 147·28]

	18-64 years		≥ 65 years	
Unit Converted to IU/mL	**GBP510 (N=834)**	**ChAdOx1-S (N=417)**	**GBP510 (N=43)**	**ChAdOx1-S (N=24)**
Ratio of GMTs (GBP510 / ChAdOx1-S)(SE)	2·95(1·06)		2·70(1·39)	
95% Confidence Interval	[2·64, 3·30]		[1·40, 5·22]	
P-value [2]	<0·0001		0·0036	
Participants with ≥ 4-fold rise, n(%)	819(98·20)	366(87·77)	41(95·35)	19(79·17)
95% Confidence Interval	[97·05, 98·99]	[84·23, 90·76]	[84·19, 99·43]	[57·85, 92·87]
Difference in Proportions of the Participant with ≥ 4-fold rise	10·43		16·18	
95% Confidence Interval	[7·35, 14·06]		[-0·51, 37·57]	
P-value [3]	<0·0001 (c)		0·09 (f)	

GMT = geometric mean titre, SD = standard deviation, SE = standard error, GMFR = geometric mean fold rise, ANCOVA = analysis of covariance, NA = not applicable.

Assay unit: IU/mL

[1] Testing for difference between treatment groups (two sample t-test).

[2] † ANCOVA model with treatment group as a factor, and baseline antibody level as covariate.

[3] Testing for difference between treatment groups (chi-square test (c)'or Fisher's exact test (f)).

GMT = anti-logarithm[mean of natural logarithm(titre at visit n)], GMFR = anti-logarithm[mean of natural logarithm(titre at visit n/titre at visit 2)].

The test result was collected for randomly selected participants (about 20% of all participants) at Visit 4.

When two samples had unequal variance, the standard deviation for the ratio of GMT is presented 'NA'.

Due to infinite likelihood problem, the variance model for adjusted GMT was fitted under the assumption of homoscedasticity.

95% confidence intervals for GMT and GMFR are calculated using Wald method with t-distribution.

The 95% CI of percentage of participants ≥ 4-fold rises was calculated based on Clopper-Pearson method.

The 95% CI of the difference between groups was calculated based on Chan and Zhang method.

Table S10. Immunogenicity Assessment by Live Virus Neutralization Assaysby (FRNT ND_{50}) up to 2 weeks after 2nd vaccination [Subgroup: Sex: Male/Female] (Per-Protocol Set)

	Male		Female	
Unit Converted to IU/mL	**GBP510 (N=530)**	**ChAdOx1-S (N=251)**	**GBP510 (N=347)**	**ChAdOx1-S (N=190)**
Baseline				
n	530	251	347	190
GMT(SD)	8·16(1·07)	8·10(1·04)	8·21(1·09)	8·16(1·07)
95% Confidence Interval	[8·11, 8·21]	[8·06, 8·14]	[8·13, 8·29]	[8·08, 8·24]
Ratio of GMTs (GBP510 / ChAdOx1-S)(SD)	1·01(NA)		1·01(NA)	
95% Confidence Interval	[1·00, 1·01]		[0·99, 1·02]	
P-value [1]	0·09		0·39	
Visit 4 (4 weeks after 1st vaccination)				
n	122	54	73	42
GMT(SD)	12·26(2·47)	36·38(3·45)	9·91(1·83)	48·97(3·46)
95% Confidence Interval	[10·42, 14·42]	[25·95, 50·99]	[8·61, 11·41]	[33·26, 72·10]
Ratio of GMTs (GBP510 / ChAdOx1-S)(SD)	0·34(NA)		0·20(NA)	
95% Confidence Interval	[0·23, 0·49]		[0·13, 0·30]	
P-value [1]	<0·0001		<0·0001	
GMFR(SD)	1·50(2·47)	4·50(3·45)	1·23(1·83)	6·00(3·36)
95% Confidence Interval	[1·28, 1·77]	[3·21, 6·31]	[1·07, 1·41]	[4·11, 8·75]
Adjusted GMT(SE)†	11·62(1·19)	34·86(1·21)	10·41(1·23)	47·23(1·23)
95% Confidence Interval	[8·29, 16·29]	[23·92, 50·81]	[6·92, 15·67]	[31·22, 71·43]
Ratio of GMTs (GBP510 / ChAdOx1-S)(SE)	0·33(1·18)		0·22(1·18)	
95% Confidence Interval	[0·24, 0·46]		[0·16, 0·30]	
P-value [2]	<0·0001		<0·0001	
Participants with ≥ 4-fold rise, n(%)	10(8·20)	29(53·70)	1(1·37)	25(59·52)
95% Confidence Interval	[4·00, 14·56]	[39·61, 67·38]	[0·03, 7·40]	[43·28, 74·37]
Difference in Proportions of the Participant with ≥ 4-fold rise	-45·51		-58·15	
95% Confidence Interval	[-59·67, -30·56]		[-72·79, -42·33]	
P-value [3]	<0·0001 ©		<0·0001 ©	
Visit 6 (2 weeks after 2nd vaccination)				
n	530	251	347	190
GMT(SD)	293·92(2·58)	98·33(2·87)	311·26(2·46)	107·57(2·61)
95% Confidence Interval	[271·05, 318·71]	[86·26, 112·10]	[283·00, 342·33]	[93·76, 123·40]
Ratio of GMTs (GBP510 / ChAdOx1-S)(SD)	2·99(NA)		2·89(2·52)	
95% Confidence Interval	[2·56, 3·49]		[2·46, 3·41]	
P-value [1]	<0·0001		<0·0001	
GMFR(SD)	36·03(2·58)	12·14(2·87)	37·91(2·48)	13·18(2·61)
95% Confidence Interval	[33·23, 39·07]	[10·64, 13·84]	[34·44, 41·72]	[11·49, 15·11]
Adjusted GMT(SE)†	304·63(1·09)	102·26(1·10)	238·90(1·10)	82·73(1·11)
95% Confidence Interval	[256·87, 361·28]	[84·54, 123·70]	[199·85, 285·58]	[67·87, 100·84]
Ratio of GMTs (GBP510 / ChAdOx1-S)(SE)	2·98(1·08)		2·89(1·09)	

	Male		Female	
Unit Converted to IU/mL	**GBP510 (N=530)**	**ChAdOx1-S (N=251)**	**GBP510 (N=347)**	**ChAdOx1-S (N=190)**
95% Confidence Interval	[2·57, 3·45]		[2·46, 3·40]	
P-value [2]	<0·0001		<0·0001	
Participants with ≥ 4-fold rise, n(%)	519(97·92)	215(85·66)	341(98·27)	170(89·47)
95% Confidence Interval	[96·32, 98·96]	[80·70, 89·75]	[96·27, 99·36]	[84·21, 93·45]
Difference in Proportions of the Participant with ≥ 4-fold rise	12·27		8·80	
95% Confidence Interval	[7·88, 17·33]		[4·44, 14·16]	
P-value [3]	<0·0001 ©		<0·0001 ©	

GMT = geometric mean titre, SD = standard deviation, SE = standard error, GMFR = geometric mean fold rise, ANCOVA = analysis of covariance, NA = not applicable.
Assay unit: IU/mL
[1] Testing for difference between treatment groups (two sample t-test).
[2] † ANCOVA model with treatment group as a factor, and baseline antibody level as covariate.
[3] Testing for difference between treatment groups (chi-square test ©'or Fisher's exact test (f)).
GMT = anti-logarithm [mean of natural logarithm (titre at visit n)], GMFR = anti-logarithm [mean of natural logarithm (titre at visit n/titre at visit 2)].
The test result was collected for randomly selected participants (about 20% of all participants) at Visit 4.
When two samples had unequal variance, the standard deviation for the ratio of GMT is presented 'NA'.
Due to infinite likelihood problem, the variance model for adjusted GMT was fitted under the assumption of homoscedasticity.
95% confidence intervals for GMT and GMFR are calculated using Wald method with t-distribution.
The 95% CI of percentage of participants ≥ 4-fold rises was calculated based on Clopper-Pearson method.
The 95% CI of the difference between groups was calculated based on Chan and Zhang method.

Table S11. The Consistency Among Ethnicities by Live Virus Neutralisation Assay (FRNT ND_{50}) up to 2 weeks after 2nd vaccination (Per Protocol Set)

Unit Converted to IU/mL	Korean		Southeast Asian		Caucasian	
	GBP510 (N=303)	**ChAdOx1-S (N=154)**	**GBP510 (N=529)**	**ChAdOx1-S (N=266)**	**GBP510 (N=45)**	**ChAdOx1-S (N=21)**
Baseline						
n	303	154	529	2	45	21
GMT(SD)	8·20(1·09)	8·14(1·07)	8·16(1·08)	8·12(1·05)	8·24(1·10)	8·08 (1·00)
95% Confidence Interval	[8·12, 8·28]	[8·06, 8·23]	[8·11, 8·21]	[8·07, 8·17]	[8·01, 8·47]	[8·08, 8.08]
Ratio of GMTs (GBP510 / ChAdOx1-S)(SD)	1·01(NA)		1·00(NA)		1.02(NA)	
95% Confidence Interval	[0.99, 1.02]		[1.00, 1.01]		[0·99, 1·05]	
P-value [1]	0·32		0·30		0·16	
Visit 6 (2 wee^{ks} after 2nd vaccination						
n	303	154	529	2	45	21
GMT(SD)	306·47(2·17)	75·26(2·54)	305·79(2·68)	131·12(2·67)	216·59(3·23)	41.12(2.48)
95% Confidence Interval	[280·82, 334·47]	[64·89, 87·29]	[281·12, 332·62]	[116·48, 147·60]	[152·29, 308·04]	[27.17, 62.21]
Ratio of GMTs (GBP510 / ChAdOx1-S)(SD)	4·07(NA)		2·33(2·67)		5·27(3.00)	
95% Confidence Interval	[3·43, 4·84]		[2·02, 2·70]		[2·95, 9·40]	
P-value [1]	<0·0001		<0·0001		<0·0001	
GMFR(SD)	37·38(2·17)	9·25(2·54)	37·47(2·68)	16·14(2·67)	26·28(3·31)	5·09(2·48)
95% Confidence Interval	[34·24, 40·80]	[7·97, 10·72]	[34·44, 40·76]	[14·34, 18·17]	[18·34, 37·67]	[3·36,7·70]
Adjusted GMT(SE)†	528·33(1·27)	129·88(1·28)	268·71(1·07)	115·88(1·09)	154·40(1·62)	28·11(1·65)
95% Confidence Interval	[328·71, 849·20]	[80·10, 210·62]	[233·68, 308·99]	[98·64, 136·12]	[59·19, 402·80]	[10·32, 76·60]
Ratio of GMTs (GBP510 / ChAdOx1-S)(SE)	4·07(1·08)		2·32(1·08)		5·49(1·31)	
95% Confidence Interval	[3·47, 4·77]		[2·01, 2·68]		[3·21, 9·38]	
P-value [2]	<0·0001		<0·0001		<0·0001	
Ratio of GMTs > 1	Yes		Yes		Yes	
Participants with ≥ 4-fold rise, n(%)	301(99·34)	124(80·52)	518(97·92)	249(93·61)	41(91·11)	157·14)
95% Confidence Interval	[97·64, 99·92]	[73·37, 86·45]	[96·31, 98·96]	[89·96, 96·23]	[78·78, 97·52]	[34·02, ·18]
Difference in Proportions of the Participant with ≥ 4-fold rise	18·82		4·31		33·97	

Unit Converted to IU/mL	Korean		Southeast Asian		Caucasian	
	GBP510 (N=303)	**ChAdOx1-S (N=154)**	**GBP510 (N=529)**	**ChAdOx1-S (N=266)**	**GBP510 (N=45)**	**ChAdOx1-S (N=21)**
95% Confidence Interval	[12·50, 25·14]		[1·13, 7·49]		[11·23, 56·71]	
P-value [4]	<0·0001 (c)		0·0019 (c)		0·0024 (f)	
Difference in Proportions of the Participant with ≥ 4-fold rise > -5%	Yes		Yes		Yes	

GMT = geometric mean titre, SD = standard deviation, SE = standard error, GMFR = geometric mean fold rise, ANCOVA = analysis of covariance, NA = not applicable.
Assay unit: IU/mL
[1] Testing for between-treatment groups (two sample t-test).
[2] † ANCOVA model with treatment group, age group (18~64, ≥65) as factors, and baseline antibody level as covariate.
[3] Testing for difference between treatment groups (chi-square test (c) or Fisher's exact test (f)).
GMT = anti-logarithm [mean of natural logarithm (titre at Visit n)], GMFR = anti-logarithm [mean of natural logarithm (titre at visit n/titre at visit 2)].
When two samples had unequal variance, the standard deviation for the ratio of GMT presented 'NA'.
95% confidence interval for GMT and GMFR are calculated using t-distribution and Confidence Interval of Seroconversion rate is calculated using Wald method.
95% confidence interval for the percentage of participants ≥ 4-fold rises was calculated by Clopper-Pearson Methods.
The 95% CI of difference in percentage of participants ≥ 4-fold rises between groups was calculated based on Wald method.

Table S12. Immunogenicity Assessment in Seropositive Participants by Live Virus Neutralization Assays (FRNT ND_{50}) Full Analysis Set

Unit Converted to IU/mL	GBP510 (N=1259)	ChAdOx1-S (N=628)
Seropositive participants	133(10·56)	66(10·51)
Baseline		
n	133	66
GMT(SD)	39·71(2·75)	41·82(2·56)
95% Confidence Interval	[33·37, 47·24]	[33·19, 52·69]
Ratio of GMTs (GBP510 / ChAdOx1-S)(SD)	0·95(2·69)	
95% Confidence Interval	[0·71, 1·27]	
P-value [1]	0·73	
Visit 4 (4 weeks after 1st vaccination)		
n	38	20
GMT(SD)	329·36(11·43)	339·79(4·81)
95% Confidence Interval	[147·87, 733·60]	[162·91, 708·74]
Ratio of GMTs (GBP510 / ChAdOx1-S)(SD)	0·97(NA)	
95% Confidence Interval	[0·34, 2·80]	
P-value [1]	0·95	
GMFR(SD)	7·11(11·35)	7·17(7·14)
95% Confidence Interval	[3·20, 15·81]	[2·86, 18·00]
Participants with ≥ 4-fold rise, n(%)	22(57·89)	12(60·00)
95% Confidence Interval	[40·82, 73·69]	[36·05, 80·88]
Difference in Proportions of the Participant with ≥ 4-fold rise	-2·11	
95% Confidence Interval	[-28·70, 24·49]	
P-value [2]	0·88 (c)	
Visit 6 (2 weeks after 2nd vaccination)		
n	127	64
GMT (SD)	989·63(4·08)	473·55(3·85)

Unit Converted to IU/mL	**GBP510 (N=1259)**	**ChAdOx1-S (N=628)**
95% Confidence Interval	[773·03, 1266·92]	[338·12, 663·21]
Ratio of GMTs (GBP510 / ChAdOx1-S)(SD)	2·09(4·00)	
95% Confidence Interval	[1·37, 3·18]	
P-value [1]	0·0007	
GMFR(SD)	24·24(5·26)	11·15(5·71)
95% Confidence Interval	[18·11, 32·45]	[7·22, 17·23]
Participants with ≥ 4-fold rise, n(%)	114(89·76)	49(76·56)
95% Confidence Interval	[83·13, 94·44]	[64·31, 86·25]
Difference in Proportions of the Participant with ≥ 4-fold rise	13·20	
95% Confidence Interval	[1·56, 24·84]	
P-value [2]	0·01 (c)	

GMT = geometric mean titre, SD = standard deviation, GMFR = geometric mean fold rise, NA = not applicable.

Assay unit: IU/mL
1. The participants with SARS-CoV-2 neutralizing antibody (by FRNT) ≥ LLOQ at baseline.
[1] Testing for between-treatment groups (two sample t-test).

[2] Testing for between-treatment groups (chi-square test (c) or Fisher's exact test (f)).

GMT = anti-logarithm [mean of natural logarithm (titre at visit n)], GMFR = anti-logarithm [mean of natural logarithm (titre at visit n/titre at visit 2)].
The test result was collected for randomly selected participants (about 20% of all participants) at Visit 4 and Visit 7.

When two samples had unequal variance, the standard deviation for the ratio of GMT is presented 'NA'.

95% confidence intervals for GMT and GMFR are calculated using Wald method with t-distribution.

The 95% CI of the difference in percentage of participants ≥ 4-fold rises between groups was calculated based on Wald method.

Table S13. Immunogenicity Assessment by Live Virus Neutralization Assays (FRNT ND_{50}) against Ancestral D614G Strain (Per-Protocol Set)

Unit: Not Converted	GBP510 (N=877)	ChAdOx1-S (N=441)
Visit 6 (2 weeks after 2nd vaccination)		
n	137	68
GMT(SD)	1666·38(2·53)	415·06(3·01)
95% Confidence Interval	[1424·54, 1949·57]	[317·84, 542·02]
Ratio of GMTs (GBP510 / ChAdOx1-S)(SD)	4·01(2·69)	
95% Confidence Interval	[3·01, 5·36]	
P-value [1]	<0·0001	

GMT = geometric mean titre, SD = standard deviation, NA = not applicable.
GMT = anti-logarithm [mean of natural logarithm (titre at visit n)].
The test result was collected for randomly selected participants (about 10% of all participants).

[1] Testing for between-treatment groups (two sample t-test).

When two samples had unequal variance, the standard deviation for the ratio of GMT is presented 'NA'.

95% confidence intervals for GMT are calculated using Wald method with t-distribution.

Table S14. Immunogenicity Assessment by Live Virus Neutralization Assays (FRNT ND_{50}) against Delta (Per-Protocol Set)

Unit: Not Converted	GBP510 (N=877)	ChAdOx1-S (N=441)
Visit 6 (2 weeks after 2nd vaccination)		
n	137	68
GMT(SD)	2644·26(2·47)	96·96(4·01)
95% Confidence Interval	[2269·54, 3080·84]	[69·29, 135·67]
Ratio of GMTs (GBP510 / ChAdOx1-S)(SD)	27·27(NA)	
95% Confidence Interval	[18·88, 39·39]	
P-value [1]	<0·0001	

GMT = geometric mean titre, SD = standard deviation, NA = not applicable.
GMT = anti-logarithm [mean of natural logarithm (titre at visit n)].
The test result was collected for randomly selected participants (about 10% of all participants).

[1] Testing for between-treatment groups (two sample t-test).

When two samples had unequal variance, the standard deviation for the ratio of GMT is presented 'NA'.

95% confidence intervals for GMT are calculated using Wald method with t-distribution.

Table S15. Immunogenicity Assessment by Live Virus Neutralizing Assays (FRNT ND_{50}) against Omicron BA.1 (Per-Protocol Set)

Unit: Not Converted	GBP510 (N=877)	ChAdOx1-S (N=441)
Visit 6 (2 weeks after 2nd vaccination)		
n	137	68
GMT(SD)	129·09(2·98)	12·27(2·05)
95% Confidence Interval	[107·36, 155·22]	[10·32, 14·59]
Ratio of GMTs (GBP510 / ChAdOx1-S)(SD)	10·52(NA)	
95% Confidence Interval	[8·18, 13·53]	
P-value [1]	<0·0001	

GMT = geometric mean titre, SD = standard deviation, NA = not applicable.
GMT = anti-logarithm [mean of natural logarithm (titre at visit n)].
The test result was collected for randomly selected participants (about 10% of all participants).
[1] Testing for between-treatment groups (two sample t-test).
When two samples had unequal variance, the standard deviation for the ratio of GMT is presented 'NA'.
95% confidence intervals for GMT are calculated using Wald method with t-distribution.

Table S16. Immunogenicity Assessment by Live Virus Neutralizing Assays (FRNT ND_{50}) against Omicron BA.5 (Per-Protocol Set)

Unit: Not Converted	GBP510 (N=877)	ChAdOx1-S (N=441)
Visit 6 (2 weeks after 2nd vaccination)		
n	137	68
GMT(SD)	61·61(2·84)	13·56(2·19)
95% Confidence Interval	[51·64, 73·51]	[11·21, 16·40]
Ratio of GMTs (GBP510 / ChAdOx1-S)(SD)	4·54(NA)	
95% Confidence Interval	[3·51, 5·88]	
P-value [1]	<0·0001	

GMT = geometric mean titre, SD = standard deviation, NA = not applicable.
GMT = anti-logarithm [mean of natural logarithm (titre at visit n)].
The test result was collected for randomly selected participants (about 10% of all participants).
[1] Testing for between-treatment groups (two sample t-test).
When two samples had unequal variance, the standard deviation for the ratio of GMT is presented 'NA'.
95% confidence intervals for GMT are calculated using Wald method with t-distribution.

Table S17. Immunogenicity Assessment by ELISA up to 2 weeks after 2nd vaccination [Subgroup: 18-64 years / ≥ 65 years]

	18-64 years		≥ 65 years	
Unit: BAU/mL	**GBP510 (N=834)**	**ChAdOx1-S (N=417)**	**GBP510 (N=43)**	**ChAdOx1-S (N=24)**
Baseline				
n	834	417	43	24
GMT(SD)	10·92(1·76)	10·73(1·70)	10·74(1·73)	11·94(1·70)
95% Confidence Interval	[10·51, 11·34]	[10·20, 11·29]	[9·07, 12·72]	[9·54, 14·95]
Ratio of GMTs (GBP510 / ChAdOx1-S)(SD)	1·02(1·74)		0·90(1·72)	
95% Confidence Interval	[0·95, 1·09]		[0·68, 1·19]	
P-value [1]	0·6021		0·4463	
Visit 4 (4 weeks after 1st vaccination)				
n	834	417	43	24
GMT(SD)	178·07(2·24)	121·70(2·39)	85·06(2·45)	86·44(2·81)
95% Confidence Interval	[168·57, 188·10]	[111·91, 132·35]	[64·55, 112·09]	[55·85, 133·80]
Ratio of GMTs (GBP510 / ChAdOx1-S)(SD)	1·46(2·29)		0·98(2·58)	
95% Confidence Interval	[1·33, 1·61]		[0·61, 1·59]	
P-value [1]	<0·0001		0·95	
GMFR(SD)	16·31(2·51)	11·34(2·65)	7·92(2·93)	7·24(3·65)
95% Confidence Interval	[15·32, 17·36]	[10·32, 12·46]	[5·69, 11·03]	[4·19, 12·51]
Adjusted GMT(SE)†	177·71(1·03)	121·96(1·04)	81·49(1·15)	86·74(1·21)
95% Confidence Interval	[168·06, 187·92]	[112·72, 131·96]	[61·14, 108·62]	[59·20, 127·09]
Ratio of GMTs (GBP510 / ChAdOx1-S)(SE)	1·46(1·05)		0·94(1·27)	
95% Confidence Interval	[1·32, 1·60]		[0·58, 1·52]	
P-value [2]	<0·0001		0·80	
Participants with ≥ 4-fold rise, n (%)	779(93·41)	360(86·33)	32(74·42)	14(58·33)
95% Confidence Interval	[91·50, 94·99]	[82·66, 89·48]	[58·83, 86·48]	[36·64, 77·89]
Difference in Proportions of the Participant with ≥ 4-fold rise	7·07		16·09	
95% Confidence Interval	[3·37, 10·78]		[-7·56, 39·73]	
P-value [3]	<0·0001 (c)		0·17 (c)	
Visit 6 (2 weeks after 2nd vaccination)				
n	834	417	43	24
GMT(SD)	3268·84(2·07)	254·97(2·17)	2567·28(2·71)	158·31(3·03)
95% Confidence Interval	[3111·14, 3434·54]	[236·63, 274·74]	[1888·41, 3490·18]	[99·18, 252·69]
Ratio of GMTs (GBP510 / ChAdOx1-S)(SD)	12·82(2·10)		16·22(2·82)	
95% Confidence Interval	[11·75, 13·99]		[9·56, 27·50]	
P-value [1]	<0·0001		<0·0001	
GMFR(SD)	299·38(2·53)	23·76(2·40)	239·07(3·49)	13·26(3·52)
95% Confidence Interval	[281·11, 318·84]	[21·84, 25·85]	[162·78, 351·11]	[7·79, 22·55]
Adjusted GMT(SE)†	3293·49(1·03)	252·42(1·04)	2289·80(1·15)	171·22(1·23)
95% Confidence Interval	[3132·45, 3462·81]	[235·26, 270·84]	[1725·18, 3039·20]	[113·90, 257·38]
Ratio of GMTs (GBP510 / ChAdOx1-S)(SE)	13·05(1·04)		13·37(1·28)	

Unit: BAU/mL	18-64 years		≥ 65 years	
	GBP510 (N=834)	**ChAdOx1-S (N=417)**	**GBP510 (N=43)**	**ChAdOx1-S (N=24)**
95% Confidence Interval	[11·97, 14·22]		[8·18, 21·86]	
P-value [2]	<0·0001		<0·0001	
Participants with ≥ 4-fold rise, n(%)	831(99·64)	407(97·60)	42(97·67)	20(83·33)
95% Confidence Interval	[98·95, 99·93]	[95·63, 98·84]	[87·71, 99·94]	[62·62, 95·26]
Difference in Proportions of the Participant with ≥ 4-fold rise	2·04		14·34	
95% Confidence Interval	[0·51, 3·56]		[-1·23, 29·92]	
P-value [3]	0·0016 (f)		0·05 (f)	

GMT = geometric mean titre, SD = standard deviation, SE = standard error, GMFR = geometric mean fold rise, ANCOVA = analysis of covariance.
Assay unit: BAU/mL
[1] Testing for difference between treatment groups (two sample t-test).
[2] † ANCOVA model with treatment group as a factor, and baseline antibody level as covariate.
[3] Testing for difference between treatment groups (chi-square test (c) or Fisher's exact test (f)).
GMT = anti-logarithm [mean of natural logarithm (titre at visit n)], GMFR = anti-logarithm [mean of natural logarithm (titre at visit n/titre at visit 2)].
95% confidence intervals for GMT and GMFR are calculated using Wald method with t-distribution.

The 95% CI of percentage of participants ≥ 4-fold rises is calculated based on Clopper-Pearson method.

The 95% CI of the difference in percentage of participants ≥ 4-fold rises between groups was calculated based on Wald method.

Table S18. Immunogenicity Assessment by ELISA up to 2 weeks after 2nd vaccination [Subgroup: Male/Female]

	Male		Female	
Unit: BAU/mL	**GBP510 (N=530)**	**ChAdOx1-S (N=251)**	**GBP510 (N=347)**	**ChAdOx1-S (N=190)**
Baseline				
n	530	251	347	190
GMT(SD)	10·64(1·75)	10·72(1·71)	11·34(1·76)	10·89(1·68)
95% Confidence Interval	[10·14, 11·16]	[10·03, 11·46]	[10·69, 12·04]	[10·11, 11·73]
Ratio of GMTs (GBP510 / ChAdOx1-S)(SD)	0·99(1·74)		1·04(1·73)	
95% Confidence Interval	[0·91, 1·08]		[0·94, 1·15]	
P-value [1]	0·85		0·41	
Visit 4 (4 weeks after 1st vaccination)				
n	530	251	347	190
GMT(SD)	153·81(2·28)	107·55(2·38)	203·22(2·23)	137·22(2·43)
95% Confidence Interval	[143·38, 165·00]	[96·58, 119·78]	[186·68, 221·22]	[120·84, 155·82]
Ratio of GMTs (GBP510 / ChAdOx1-S)(SD)	1·43(2·31)		1·48(2·30)	
95% Confidence Interval	[1·26, 1·62]		[1·28, 1·72]	
P-value [1]	<0·0001		<0·0001	
GMFR(SD)	14·46(2·53)	10·03(2·64)	17·92(2·58)	12·60(2·79)
95% Confidence Interval	[13·36, 15·66]	[8·89, 11·32]	[16·21, 19·80]	[10·88, 14·59]
Adjusted GMT(SE)†	122·60(1·07)	86·13(1·08)	145·35(1·08)	99·17(1·09)
95% Confidence Interval	[106·39, 141·27]	[73·50, 100·92]	[123·99, 170·39]	[83·10, 118·36]
Ratio of GMTs (GBP510 / ChAdOx1-S)(SE)	1·42(1·06)		1·47(1·08)	
95% Confidence Interval	[1·26, 1·61]		[1·27, 1·69]	
P-value [2]	<0·0001		<0·0001	
Participants with ≥ 4-fold rise, n(%)	485(91·51)	208(82·87)	326(93·95)	166(87·37)
95% Confidence Interval	[88·80, 93·74]	[77·63, 87·32]	[90·90, 96·22]	[81·79, 91·74]
Difference in Proportions of the Participant with ≥ 4-fold rise	8·64		6·58	
95% Confidence Interval	[3·41, 13·87]		[1·23, 11·93]	
P-value [3]	0·0004 (c)		0·0085 (c)	
			32(74·42)	14(58·33)
Visit 6 (2 weeks after 2nd vaccination)				
n	530	251	347	190
GMT(SD)	3163·96(2·11)	229·07(2·15)	3334·46(2·09)	276·57(2·32)
95% Confidence Interval	[2968·08, 3372·76]	[208·27, 251·95]	[3084·90, 3604·22]	[245·25, 311·89]
Ratio of GMTs (GBP510 / ChAdOx1-S)(SD)	13·81(2·13)		12·06(NA)	
95% Confidence Interval	[12·33, 15·47]		[10·45, 13·91]	
P-value [1]	<0·0001		<0·0001	
GMFR(SD)	297·50(2·55)	21·37(2·40)	293·96(2·61)	25·39(2·58)
95% Confidence Interval	[274·66, 322·25]	[19·17, 23·82]	[265·62, 325·34]	[22·17, 29·09]
Adjusted GMT(SE)†	2976·65(1·07)	212·21(1·08)	2723·44(1·08)	220·61(1·09)
95% Confidence Interval	[2617·27, 3385·38]	[183·77, 245·06]	[2349·82, 3156·47]	[187·27, 259·87]
Ratio of GMTs (GBP510 / ChAdOx1-S)(SE)	14·03(1·06)		12·35(1·07)	

	Male		Female	
Unit: BAU/mL	**GBP510 (N=530)**	**ChAdOx1-S (N=251)**	**GBP510 (N=347)**	**ChAdOx1-S (N=190)**
95% Confidence Interval	[12·54, 15·68]		[10·80, 14·11]	
P-value [2]	<0·0001		<0·0001	
Participants with ≥ 4-fold rise, n(%)	527(99·43)	242(96·41)	346(99·71)	185(97·37)
95% Confidence Interval	[98·35, 99·88]	[93·30, 98·35]	[98·40, 99·99]	[93·97, 99·14]
Difference in Proportions of the Participant with ≥ 4-fold rise	3·02		2·34	
95% Confidence Interval	[0·63, 5·41]		[-0·00, 4·69]	
P-value [3]	0·0027 (f)		0·02 (f)	

GMT = geometric mean titre, SD = standard deviation, SE = standard error, GMFR = geometric mean fold rise, ANCOVA = analysis of covariance.
Assay unit: BAU/mL
[1] Testing for difference between treatment groups (two sample t-test).
[2] † ANCOVA model with treatment group as a factor, and baseline antibody level as covariate.
[3] Testing for difference between treatment groups (chi-square test (c) or Fisher's exact test (f)).
GMT = anti-logarithm [mean of natural logarithm (titre at visit n)], GMFR = anti-logarithm [mean of natural logarithm (titre at visit n/titre at visit 2)].
95% confidence intervals for GMT and GMFR are calculated using Wald method with t-distribution.

The 95% CI of percentage of participants ≥ 4-fold rises is calculated based on Clopper-Pearson method.

The 95% CI of the difference in percentage of participants ≥ 4-fold rises between groups was calculated based on Wald method.

Table S19. Cell-mediated Response Assessed for CD8+ T cells expressing cytokines by ICS (Per-Protocol Set)

	GBP510 (N=877)	ChAdOx1-S (N=441)
[cytokines: IFNγ]		
Baseline		
n	70	36
Mean (SD)	0 (0·01)	0· (0)
Median	0	0
IQR	0-0·01	0-0·01
Min, Max	0, 0·05	0, 0·02
P-value [1]	0·31	
Visit 6 (2 weeks after 2nd vaccination)		
n	68	33
Mean (SD)	0·01(0·02)	0·01(0·01)
Median	0	0·01
IQR	0 -0·01	0 -0·01
Min, Max	0, 0·15	0, 0·06
P-value [1]	0·84	
[cytokines: IL-2]		
Baseline		
n	70	36
Mean (SD)	0 (0·01)	0 (0·01)
Median	0	0
IQR	0 -0·01	0 -0
Min, Max	0, 0·05	0, 0·06
P-value [1]	0·61	
Visit 6 (2 weeks after 2nd vaccination)		
n	68	33
Mean (SD)	0 (0·01)	0·01(0·01)
Median	0	0
IQR	0 -0·01	0 -0·01
Min, Max	0, 0·08	0, 0·03
P-value [1]	0·48	
[cytokines: IL-4]		
Baseline		
n	70	36
Mean (SD)	0·01(0·01)	0·01(0·01)
Median	0	0
IQR	0 -0·01	0 -0·01
Min, Max	0, 0·07	0, 0·04
P-value [1]	0·98	
Visit 6 (2 weeks after 2nd vaccination)		
n	68	33
Mean (SD)	0·01(0·01)	0 (0·01)
Median	0	0
IQR	0 -0·01	0 -0·01
Min, Max	0, 0·06	0, 0·03
P-value [1]	0·47	
[cytokines: TNFα]		
Baseline		
n	70	36
Mean (SD)	0·04(0·12)	0·04(0·12)

	GBP510 (N=877)	ChAdOx1-S (N=441)
Median	0·02	0·02
IQR	0 -0·04	0 -0·03
Min, Max	0, 0·88	0, 0·73
P-value [1]	0·98	
Visit 6 (2 weeks after 2nd vaccination)		
n	68	33
Mean (SD)	0·11(0·26)	0·07(0·13)
Median	0·02	0·02
IQR	0 -0·09	0 -0·06
Min, Max	0, 1·66	0, 0·57
P-value [1]	0·27	

SD = standard deviation, IQR = Interquartile range, Min = minimum, Max = maximum, CMI = cell medicated immunity.
Assay unit: % of RBD-specific CD8+ T cells
[1] Testing for difference between treatment groups (two sample t-test).
The test result was collected for randomly selected participants (about 10% of all participants).

Table S20. Overall Adverse Events – by each cohort up to 28 days after 2nd vaccination (Safety Set) [after any vaccination]

	Cohort 1		Cohort 2	
	GBP510 (N=1,298)	**ChAdOx1-S (N=650)**	**GBP510 (N=1,731)**	**ChAdOx1-S (N=346)**
Adverse Events after any vaccine injection				
Participants with Immediate Unsolicited AEs	2(0·15) [2]	0(0·00) [0]	4(0·23) [5]	0(0·00) [0]
95% Confidence Interval	[0·02, 0·56]	[0·00, 0·57]	[0·06, 0·59]	[0·00, 1·06]
Participants with Immediate Unsolicited ADRs	2(0·15) [2]	0(0·00) [0]	3(0·17) [4]	0(0·00) [0]
95% Confidence Interval	[0·02, 0·56]	[0·00, 0·57]	[0·04, 0·51]	[0·00, 1·06]
Solicited reaction within 7 days after vaccination				
Participants with Solicited Local AEs	936(72·11) [1,715]	356(54·77) [502]	781(45·12) [1,231]	134(38·73) [175]
95% Confidence Interval	[69·58, 74·54]	[50·85, 58·64]	[42·76, 47·50]	[33·57, 44·08]
Participants with Solicited Systemic AEs	864(66·56) [3,749]	412(63·38) [1,656]	687(39·69) [2,384]	121(34·97) [411]
95% Confidence Interval	[63·92, 69·13]	[59·55, 67·10]	[37·37, 42·04]	[29·95, 40·25]
Within 28 days after vaccination				
Participants with Unsolicited AEs	248(19·11) [423]	120(18·46) [174]	154(8·90) [217]	25(7·23) [39]
95% Confidence Interval	[17·00, 21·35]	[15·55, 21·66]	[7·60, 10·34]	[4·73, 10·48]
Participants with Unsolicited ADRs	79(6·09) [130]	36(5·54) [51]	27(1·56) [34]	5(1·45) [8]
95% Confidence Interval	[4·85, 7·53]	[3·91, 7·59]	[1·03, 2·26]	[0·47, 3·34]
Participants with SAEs	10(0·77) [10]	4(0·62) [5]	5(0·29) [5]	3(0·87) [4]
95% Confidence Interval	[0·37, 1·41]	[0·17, 1·57]	[0·09, 0·67]	[0·18, 2·51]

	Cohort 1		Cohort 2	
	GBP510 (N=1,298)	**ChAdOx1-S (N=650)**	**GBP510 (N=1,731)**	**ChAdOx1-S (N=346)**
Participants with AESIs	0(0·00) [0]	1(0·15) [1]	2(0·12) [2]	0(0·00) [0]
95% Confidence Interval	[0·00, 0·28]	[0·00, 0·85]	[0·01, 0·42]	[0·00, 1·06]
Participants with MAAEs	73(5·62) [97]	38(5·85) [54]	74(4·27) [75]	12(3·47) [15]
95% Confidence Interval	[4·43, 7·02]	[4·17, 7·94]	[3·37, 5·34]	[1·80, 5·98]
Participants with MAADRs	13(1·00) [21]	9(1·38) [16]	4(0·23) [4]	1(0·29) [2]
95% Confidence Interval	[0·53, 1·71]	[0·64, 2·61]	[0·06, 0·59]	[0·01, 1·60]
Participants with AEs leading to study withdrawal*	0(0·00) [0]	0(0·00) [0]	3(0·17) [8]	2(0·58) [3]
95% Confidence Interval	[0·00, 0·28]	[0·00, 0·57]	[0·04, 0·51]	[0·07, 2·07]
Participants with AEs leading to death**	0(0·00) [0]	1(0·15) [1]	0(0·00) [0]	0(0·00) [0]
95% Confidence Interval	[0·00, 0·28]	[0·00, 0·85]	[0·00, 0·21]	[0·00, 1·06]

AEs = adverse events, ADRs= adverse drug reactions, SAEs = serious adverse events, AESIs = adverse events of special interest, MAAEs = medically attended adverse events, MAADRs = medically attended adverse drug reactions.

Data are presented as 'number of participants (% participants) [number of events]'. Denominator of percentage is the number of participants in each group. 95% confidence interval was calculated by Clopper-Pearson Methods.

* The case checked on 'at the discretion of the investigator or sponsor due to safety concerns' as a primary reason for discontinuation and checked on 'Stop Vaccination (only if, prior to 2nd vaccination)' as changes to IP vaccination.

** The case checked on 'Death' as a primary reason for discontinuation and checked on 'Fatal' as outcome.

Table S21. Solicited Local AE by Maximum severity [after any vaccination] (Safety Set)

	GBP510 (N=3029)				ChAdOx1-S (N=996)			
	Grade 1 (Mild)	**Grade 2 (Moderate)**	**Grade 3 (Severe)**	**Grade 4 (Potentially Life Threatening)**	**Grade 1 (Mild)**	**Grade 2 (Moderate)**	**Grade 3 (Severe)**	**Grade 4 (Potentially Life Threatening)**
Adverse Events after any vaccination, n (%)								
Injection Site Pain	1348(44·50)	293(9·67)	46(1·52)	0	414(41·57)	66(6·63)	6(0·60)	0
Injection Site Redness	101(3·33)	49(1·62)	9(0·30)	0	20(2·01)	0	0	0
Injection Site Swelling	123(4·06)	42(1·39)	3(0·10)	0	11(1·10)	1(0·10)	0	0

Note: Denominator of percentage is the number of participants in each group.
Adverse events are displayed as 'number of participants (percentage of participants)'.
If one subject experienced the same adverse event more than once, the adverse event is counted only once with the most severe category.

Table S22. Solicited Systemic AEs by Maximum Severity [after any vaccination] (Safety Set)

	GBP510 (N=3029)				ChAdOx1-S (N=996)			
	Grade 1 (Mild)	**Grade 2 (Moderate)**	**Grade 3 (Severe)**	**Grade 4 (Potentially Life Threatening)**	**Grade 1 (Mild)**	**Grade 2 (Moderate)**	**Grade 3 (Severe)**	**Grade 4 (Potentially Life Threatening)**
Adverse Events after any vaccination, n (%)								
Fever	260(8·58)	159(5·25)	55(1·82)	0	88(8·84)	45(4·52)	28(2·81)	1(0·10)
Nausea/Vomiting	178(5·88)	25(0·83)	0	0	63(6·33)	14(1·41)	1(0·10)	0
Diarrhea	136(4·49)	28(0·92)	3(0·10)	0	70(7·03)	10(1·00)	0	0
Headache	680(22·45)	200(6·60)	25(0·83)	0	258(25·90)	65(6·53)	8(0·80)	0
Fatigue	626(20·67)	253(8·35)	62(2·05)	0	205(20·58)	101(10·14)	21(2·11)	0
Myalgia	553(18·26)	306(10·10)	64(2·11)	0	198(19·88)	94(9·44)	15(1·51)	0
Arthralgia	295(9·74)	126(4·16)	26(0·86)	0	120(12·05)	48(4·82)	8(0·80)	0
Chills	456(15·05)	180(5·94)	49(1·62)	0	155(15·56)	70(7·03)	21(2·11)	0

Note: Denominator of percentage is the number of participants in each group.
Adverse events are displayed as 'number of participants (percentage of participants)'.
If one subject experienced the same adverse event more than once, the adverse event is counted only once with the most severe category.

Table S23. Unsolicited AE [after any vaccination] (Safety Set): up to 4 weeks after 2nd vaccination

	GBP510 (N=3029)	ChAdOx1-S (N=996)	Total (N=4025)
Participants with Unsolicited AEs	402(13·27) [640]	145(14·56) [213]	547(13·59) [853]
Exact 95% Confidence Interval	[12·08, 14·53]	[12·43, 16·90]	[12·55, 14·69]
P-value [1]			0·30 (c)
Severity			
Grade 0 (None)	58(9·06)	23(10·80)	81(9·50)
Grade 1 (Mild)	414(64·69)	121(56·81)	535(62·72)
Grade 2 (Moderate)	141(22·03)	51(23·94)	192(22·51)
Grade 3 (Severe)	26(4·06)	18(8·45)	44(5·16)
Grade 4 (Potentially Life Threatening)	1(0·16)	0	1(0·12)
Serious AE			
Yes	15(2·34)	9(4·23)	24(2·81)
No	625(97·66)	204(95·77)	829(97·19)
MAAE			
Hospitalization	14(8·64)	8(13·56)	22(9·95)
ER visit	10(6·17)	1(1·69)	11(4·98)
Other visit to a healthcare professional	138(85·19)	50(84·75)	188(85·07)
AESI			
Yes	2(0·31)	1(0·47)	3(0·35)
No	638(99·69)	212(99·53)	850(99·65)
Outcome			
Recovered/Resolved	568(88·75)	191(89·67)	759(88·98)
Recovering/Resolving	38(5·94)	11(5·16)	49(5·74)
Not recovered/Not Resolved	30(4·69)	7(3·29)	37(4·34)
Stabilized	27(4·22)	6(2·82)	33(3·87)
Not stabilized	3(0·47)	1(0·47)	4(0·47)
Recovered/Resolved with sequelae	0	0	0
Fatal	0	1(0·47)	1(0·12)
Unknown	4(0·63)	3(1·41)	7(0·82)
Causality			
Related	164(25·63)	59(27·70)	223(26·14)
Not-related	476(74·38)	154(72·30)	630(73·86)
Changes to IP vaccination			
Stop Vaccination (only if, prior to 2nd vaccination)	87(13·59)	23(10·80)	110(12·90)
Continue to Vaccination (only if, prior to 2nd vaccination)	268(41·88)	111(52·11)	379(44·43)
Unknown	0	0	0
Not Applicable (only if, after 2nd vaccination)	285(44·53)	79(37·09)	364(42·67)
Medication			
Yes	305(47·66)	108(50·70)	413(48·42)
No	335(52·34)	105(49·30)	440(51·58)
Participants with Unsolicited ADRs	106(3·50) [164]	41(4·12) [59]	147(3·65) [223]
Exact 95% Confidence Interval	[2·87, 4·22]	[2·97, 5·54]	[3·09, 4·28]
P-value [1]			0·37 (c)

	GBP510 (N=3029)	ChAdOx1-S (N=996)	Total (N=4025)
Severity			
Grade 0 (None)	0	0	0
Grade 1 (Mild)	120(73·17)	41(69·49)	161(72·20)
Grade 2 (Moderate)	40(24·39)	15(25·42)	55(24·66)
Grade 3 (Severe)	4(2·44)	3(5·08)	7(3·14)
Grade 4 (Potentially Life Threatening)	0	0	0
Serious ADR			
Yes	1(0·61)	0	1(0·45)
No	163(99·39)	59(100·00)	222(99·55)
MAAE			
Hospitalization	1(6·67)	0	1(4·35)
ER visit	0	0	0
Other visit to a healthcare professional	14(93·33)	8(100·00)	22(95·65)
AESI			
Yes	1(0·61)	0	1(0·45)
No	163(99·39)	59(100·00)	222(99·55)
Outcome			
Recovered/Resolved	151(92·07)	55(93·22)	206(92·38)
Recovering/Resolving	9(5·49)	2(3·39)	11(4·93)
Not recovered/Not Resolved	4(2·44)	2(3·39)	6(2·69)
Stabilized	4(2·44)	2(3·39)	6(2·69)
Not stabilized	0	0	0
Recovered/Resolved with sequelae	0	0	0
Fatal	0	0	0
Unknown	0	0	0
Changes to IP vaccination			
Stop Vaccination (only if, prior to 2nd vaccination)	2(1·22)	0	2(0·90)
Continue to Vaccination (only if, prior to 2nd vaccination)	83(50·61)	45(76·27)	128(57·40)
Unknown	0	0	0
Not Applicable (only if, after 2nd vaccination)	79(48·17)	14(23·73)	93(41·70)
Medication			
Yes	43(26·22)	16(27·12)	59(26·46)
No	121(73·78)	43(72·88)	164(73·54)

AEs = adverse events, ADRs= adverse drug reactions, MAAEs = medically attended adverse events, AESIs = adverse events of special interest, IP = investigator product, ER = emergency room

Data are presented as 'number of participants (% participants) [number of events]'. Denominator of percentage is the number of participants in each group. 95% confidence interval was calculated by Clopper-Pearson Methods. Asymptomatic COVID-19 cases that symptom was 'No' in the [COVID-19 related Information] page of eCRF and symptom is not recorded on SAFETY DB were categorized as 'Grade 0 (None)'.

[1] Testing for between-treatment groups (chi-square test (c) or Fisher's exact test (f)).

Table S24. Overall Adverse Events (Safety Set) [Subgroup: Age Group: 18-64 years/≥ 65 years]: up to 4 weeks after 2nd vaccination

	18-64 years		≥ 65 years	
Adverse Events after any vaccine injection	**GBP510 (N=2871)**	**ChAdOx1-S (N=941)**	**GBP51 (N=158)**	**ChAdOx1-S (N=55)**
Participants with Immediate Unsolicited AEs	6(0·21) [7]	0	0	0
Exact 95% Confidence Interval	[0·08, 0·45]	[0·00, 0·39]	[0·00, 2·31]	[0·00, 6·49]
Participants with Immediate Unsolicited ADRs	5(0·17) [6]	0	0	0
Exact 95% Confidence Interval	[0·06, 0·41]	[0·00, 0·39]	[0·00, 2·31]	[0·00, 6·49]
Solicited reaction within 7 days after vaccination				
Participants with Solicited Local AEs	1628(56·70) [2814]	465(49·42) [645]	89(56·33) [132]	25(45·45) [32]
Exact 95% Confidence Interval	[54·87, 58·53]	[46·17, 52·66]	[482, 64·19]	[31·97, 59·45]
Participants with Solicited Systemic AEs	1476(51·41) [5903]	505(53·67) [1979]	75(47·47) [230]	28(50·91) [88]
Exact 95% Confidence Interval	[49·56, 53·25]	[50·42, 56·89]	[39·48, 55·55]	[37·07, 64·65]
Within 28 days after vaccination				
Participants with Unsolicited AEs	379(13·20) [613]	137(14·56) [204]	23(14·56) [27]	8(14·55) [9]
Exact 95% Confidence Interval	[11·98, 14·49]	[12·37, 16·98]	[46, 21·04]	[6·50, 26·66]
Participants with Unsolicited ADRs	103(3·59) [161]	40(4·25) [58]	3(1·90) [3]	1(1·82) [1]
Exact 95% Confidence Interval	[2·94, 4·33]	[3·05, 5·74]	[0·39, 5·45]	[0·05, 9·72]
Participants with SAEs	14(0·49) [14]	6(0·64) [8]	1(0·63) [1]	1(1·82) [1]
Exact 95% Confidence Interval	[0·27, 0·82]	[0·23, 1·38]	[0·02, 3·48]	[0·05, 9·72]
Participants with AESIs	2(0·07) [2]	1(0·11) [1]	0	0
Exact 95% Confidence Interval	[0·01, 0·25]	[0·00, 0·59]	[0·00, 2·31]	[0·00, 6·49]
Participants with MAAEs	142(4·95) [166]	47(4·99) [66]	5(3·16) [6]	3(5·45) [3]
Exact 95% Confidence Interval	[4·18, 5·80]	[3·69, 6·59]	[1·04, 7·23]	[1·14, 15·12]
Participants with MAADRs	17(0·59) [25]	10(1·06) [18]	0	0
Exact 95% Confidence Interval	[0·35, 0·95]	[0·51, 1·95]	[0·00, 2·31]	[0·00, 6·49]
Participants with AEs leading to study withdrawal*	3(0·10) [8]	2(0·21) [3]	0	0
Exact 95% Confidence Interval	[0·02, 0·31]	[0·03, 0·77]	[0·00, 2·31]	[0·00, 6·49]
Participants with AEs leading to death**	0	1(0·11) [1]	0	0
Exact 95% Confidence Interval	[0·00, 0·13]	[0·00, 0·59]	[0·00, 2·31]	[0·00, 6·49]

AEs = adverse events, ADRs= adverse drug reactions, MAAEs = medically attended adverse events, SAEs = serious adverse events,
SADRs = serious adverse drug reactions, AESIs = adverse events of special interest.
Data are presented as 'number of participants (% participants) [number of events]'. Denominator of percentage is the number of participants in each group. 95% confidence interval was calculated by Clopper-Pearson Methods.
* The case checked on 'at the discretion of the investigator or sponsor due to safety concerns' as a primary reason for discontinuation and checked on 'Stop Vaccination (only if, prior to 2nd vaccination)' as changes to IP vaccination.
** The case checked on 'Death' as a primary reason for discontinuation and checked on 'Fatal' as outcome.

Table S25. Overall Adverse Events (Safety Set) [Subgroup: Male/Female]: up to 4 weeks after 2nd vaccination

	MALE		FEMALE	
Adverse Events after any vaccine injection	**GBP510 (N=1807)**	**ChAdOx1-S (N=572)**	**GBP510 (N=1222)**	**ChAdOx1-S (N=424)**
Participants with Immediate Unsolicited AEs	1(0·06) [1]	0	5(0·41) [6]	0
Exact 95% Confidence Interval	[0·00, 0·31]	[0·00, 0·64]	[0·13, 0·95]	[0·00, 0·87]
Participants with Immediate Unsolicited ADRs	1(0·06) [1]	0	4(0·33) [5]	0
Exact 95% Confidence Interval	[0·00, 0·31]	[0·00, 0·64]	[0·09, 0·84]	[0·00, 0·87]
'Solicited reaction within 7 days after vaccination				
Participants with Solicited Local AEs	984(54·45) [1659]	262(45·80) [358]	733(59·98) [1287]	228(53·77) [319]
Exact 95% Confidence Interval	[52·13, 56·77]	[41·66, 49·99]	[577, 62·74]	[48·90, 58·60]
Participants with Solicited Systemic AEs	860(47·59) [3267]	288(50·35) [1085]	691(56·55) [2866]	245(57·78) [982]
Exact 95% Confidence Interval	[45·27, 49·93]	[46·17, 54·52]	[53·71, 59·35]	[52·92, 62·53]
Within 28 days after vaccination				
Participants with Unsolicited AEs	223(12·34) [321]	72(12·59) [101]	179(14·65) [319]	73(17·22) [112]
Exact 95% Confidence Interval	[10·86, 13·95]	[9·98, 15·59]	[121, 16·76]	[13·75, 21·15]
Participants with Unsolicited ADRs	51(2·82) [80]	22(3·85) [35]	55(4·50) [84]	19(4·48) [24]
Exact 95% Confidence Interval	[2·11, 3·69]	[2·43, 5·77]	[3·41, 5·82]	[2·72, 6·91]
Participants with SAEs	10(0·55) [10]	4(0·70) [5]	5(0·41) [5]	3(0·71) [4]
Exact 95% Confidence Interval	[0·27, 1·02]	[0·19, 1·78]	[0·13, 0·95]	[0·15, 2·05]
Participants with AESIs	2(0·11) [2]	1(0·17) [1]	0	0
Exact 95% Confidence Interval	[0·01, 0·40]	[0·00, 0·97]	[0·00, 0·30]	[0·00, 0·87]
Participants with MAAEs	90(4·98) [103]	28(4·90) [40]	57(4·66) [69]	22(5·19) [29]
Exact 95% Confidence Interval	[4·02, 6·09]	[3·28, 7·00]	[3·55, 6·00]	[3·28, 7·75]
Participants with MAADRs	9(0·50) [15]	7(1·22) [15]	8(0·65) [10]	3(0·71) [3]
Exact 95% Confidence Interval	[0·23, 0·94]	[0·49, 2·51]	[0·28, 1·29]	[0·15, 2·05]
Participants with AEs leading to study withdrawal*	3(0·17) [8]	0	0	2(0·47) [3]
Exact 95% Confidence Interval	[0·03, 0·48]	[0·00, 0·64]	[0·00, 0·30]	[0·06, 1·69]
Participants with AEs leading to death**	0	1(0·17) [1]	0	0
Exact 95% Confidence Interval	[0·00, 0·20]	[0·00, 0·97]	[0·00, 0·30]	[0·00, 0·87]

AEs = adverse events, ADRs= adverse drug reactions, MAAEs = medically attended adverse events, SAEs = serious adverse events,
SADRs = serious adverse drug reactions, AESIs = adverse events of special interest.
Data are presented as 'number of participants (% participants) [number of events]'. Denominator of percentage is the number of participants in each group. 95% confidence interval was calculated by Clopper-Pearson Methods.
* The case checked on 'at the discretion of the investigator or sponsor due to safety concerns' as a primary reason for discontinuation and checked on 'Stop Vaccination (only if prior to 2nd vaccination)' as changes to IP vaccination.
** The case checked on 'Death' as a primary reason for discontinuation and checked on 'Fatal' as outcome.

Table S26. Incidence of MAAEs by System Organ Class / Preferred Term Safety Set [up to 4 weeks after 2nd vaccination]

System organ class Preferred term	GBP510 (N=3029)	ChAdOx1-S (N=996)	Total (N=4025)
Participants with MAAEs	147(4·85) [172]	50(5·02) [69]	197(4·89) [241]
Exact 95% Confidence Interval	[4·12, 5·68]	[3·75, 6·57]	[4·25, 5·61]
P-value [1]			0·83 (c)
Solicited Local MAAEs			
Injection Site Pain	0	0	0
Injection Site Redness	0	0	0
Injection Site Swelling	0	0	0
Solicited Systemic MAAEs			
Fever	1(0·03) [1]	2(0·20) [2]	3(0·07) [3]
Nausea/Vomiting	1(0·03) [1]	1(0·10) [1]	2(0·05) [2]
Diarrhea	0	0	0
Headache	1(0·03) [1]	1(0·10) [1]	2(0·05) [2]
Fatigue	2(0·07) [2]	1(0·10) [1]	3(0·07) [3]
Myalgia	3(0·10) [3]	3(0·30) [3]	6(0·15) [6]
Arthralgia	1(0·03) [1]	1(0·10) [1]	2(0·05) [2]
Chills	1(0·03) [1]	1(0·10) [1]	2(0·05) [2]
Unsolicited MAAEs			
Infections and infestations	85(2·81) [86]	21(2·11) [22]	106(2·63) [108]
Suspected COVID-19	33(1·09) [33]	5(0·50) [5]	38(0·94) [38]
COVID-19	24(0·79) [24]	9(0·90) [9]	33(0·82) [33]
Upper respiratory tract infection	8(0·26) [8]	1(0·10) [1]	9(0·22) [9]
Nasopharyngitis	2(0·07) [2]	2(0·20) [2]	4(0·10) [4]
Systemic viral infection	3(0·10) [3]	0	3(0·07) [3]
Conjunctivitis	2(0·07) [2]	0	2(0·05) [2]
Rhinitis	1(0·03) [1]	1(0·10) [1]	2(0·05) [2]
Tonsillitis	1(0·03) [1]	1(0·10) [1]	2(0·05) [2]
Urinary tract infection	2(0·07) [2]	0	2(0·05) [2]
Anal abscess	1(0·03) [1]	0	1(0·02) [1]
Appendicitis	1(0·03) [1]	0	1(0·02) [1]
Cystitis	0	1(0·10) [1]	1(0·02) [1]
Gastroenteritis	1(0·03) [1]	0	1(0·02) [1]
Herpes virus infection	0	1(0·10) [1]	1(0·02) [1]
Laryngopharyngitis	1(0·03) [1]	0	1(0·02) [1]
Latent tuberculosis	1(0·03) [1]	0	1(0·02) [1]
Localised infection	1(0·03) [1]	0	1(0·02) [1]
Nail infection	1(0·03) [1]	0	1(0·02) [1]
Otitis externa	0	1(0·10) [1]	1(0·02) [1]
Peritonsillitis	1(0·03) [1]	0	1(0·02) [1]
Pneumonia	1(0·03) [1]	0	1(0·02) [1]
Tinea pedis	1(0·03) [1]	0	1(0·02) [1]
Musculoskeletal and connective tissue disorders	16(0·53) [16]	7(0·70) [8]	23(0·57) [24]
Arthralgia	3(0·10) [3]	1(0·10) [1]	4(0·10) [4]
Myalgia	3(0·10) [3]	1(0·10) [1]	4(0·10) [4]
Pain in extremity	3(0·10) [3]	0	3(0·07) [3]
Back pain	2(0·07) [2]	0	2(0·05) [2]

System organ class Preferred term	GBP510 (N=3029)	ChAdOx1-S (N=996)	Total (N=4025)
Rotator cuff syndrome	1(0·03) [1]	1(0·10) [1]	2(0·05) [2]
Temporomandibular joint syndrome	1(0·03) [1]	1(0·10) [1]	2(0·05) [2]
Fibromyalgia	0	1(0·10) [2]	1(0·02) [2]
Costochondritis	1(0·03) [1]	0	1(0·02) [1]
Flank pain	1(0·03) [1]	0	1(0·02) [1]
Intervertebral disc protrusion	0	1(0·10) [1]	1(0·02) [1]
Muscle oedema	1(0·03) [1]	0	1(0·02) [1]
Soft tissue mass	0	1(0·10) [1]	1(0·02) [1]
Gastrointestinal disorders	7(0·23) [7]	8(0·80) [9]	15(0·37) [16]
Gastroesophageal reflux disease	1(0·03) [1]	3(0·30) [3]	4(0·10) [4]
Gastritis	1(0·03) [1]	1(0·10) [1]	2(0·05) [2]
Abdominal pain	0	1(0·10) [1]	1(0·02) [1]
Abdominal pain upper	0	1(0·10) [1]	1(0·02) [1]
Colitis	1(0·03) [1]	0	1(0·02) [1]
Dyspepsia	0	1(0·10) [1]	1(0·02) [1]
Gingival bleeding	1(0·03) [1]	0	1(0·02) [1]
Haematochezia	1(0·03) [1]	0	1(0·02) [1]
Haemorrhoids	1(0·03) [1]	0	1(0·02) [1]
Nausea	1(0·03) [1]	0	1(0·02) [1]
Pancreatitis acute	0	1(0·10) [1]	1(0·02) [1]
Stomatitis	0	1(0·10) [1]	1(0·02) [1]
Injury, poisoning and procedural complications	11(0·36) [11]	2(0·20) [2]	13(0·32) [13]
Skin laceration	4(0·13) [4]	0	4(0·10) [4]
Hand fracture	2(0·07) [2]	0	2(0·05) [2]
Epicondylitis	1(0·03) [1]	0	1(0·02) [1]
Joint injury	1(0·03) [1]	0	1(0·02) [1]
Limb injury	0	1(0·10) [1]	1(0·02) [1]
Muscle strain	1(0·03) [1]	0	1(0·02) [1]
Post-traumatic pain	1(0·03) [1]	0	1(0·02) [1]
Skin abrasion	0	1(0·10) [1]	1(0·02) [1]
Wound	1(0·03) [1]	0	1(0·02) [1]
General disorders and administration site conditions	7(0·23) [8]	5(0·50) [5]	12(0·30) [13]
Chest pain	3(0·10) [3]	2(0·20) [2]	5(0·12) [5]
Pain	3(0·10) [3]	0	3(0·07) [3]
Chest discomfort	0	1(0·10) [1]	1(0·02) [1]
Chills	1(0·03) [1]	0	1(0·02) [1]
Facial discomfort	0	1(0·10) [1]	1(0·02) [1]
Fatigue	0	1(0·10) [1]	1(0·02) [1]
Pyrexia	1(0·03) [1]	0	1(0·02) [1]
Respiratory, thoracic and mediastinal disorders	5(0·17) [9]	2(0·20) [5]	7(0·17) [14]
Cough	4(0·13) [4]	1(0·10) [1]	5(0·12) [5]
Rhinorrhoea	2(0·07) [2]	2(0·20) [2]	4(0·10) [4]
Oropharyngeal pain	1(0·03) [1]	2(0·20) [2]	3(0·07) [3]
Asthma	1(0·03) [1]	0	1(0·02) [1]
Productive cough	1(0·03) [1]	0	1(0·02) [1]
Nervous system disorders	6(0·20) [6]	0	6(0·15) [6]
Headache	2(0·07) [2]	0	2(0·05) [2]
Dizziness	1(0·03) [1]	0	1(0·02) [1]
Migraine	1(0·03) [1]	0	1(0·02) [1]
Paraesthesia	1(0·03) [1]	0	1(0·02) [1]
Syncope	1(0·03) [1]	0	1(0·02) [1]
Skin and subcutaneous tissue disorders	5(0·17) [5]	1(0·10) [1]	6(0·15) [6]

System organ class Preferred term	GBP510 (N=3029)	ChAdOx1-S (N=996)	Total (N=4025)
Urticaria	3(0·10) [3]	1(0·10) [1]	4(0·10) [4]
Dermatitis atopic	1(0·03) [1]	0	1(0·02) [1]
Rash	1(0·03) [1]	0	1(0·02) [1]
Renal and urinary disorders	2(0·07) [2]	2(0·20) [2]	4(0·10) [4]
Ureterolithiasis	1(0·03) [1]	1(0·10) [1]	2(0·05) [2]
Glomerulonephritis rapidly progressive	1(0·03) [1]	0	1(0·02) [1]
Proteinuria	0	1(0·10) [1]	1(0·02) [1]
Surgical and medical procedures	3(0·10) [3]	1(0·10) [1]	4(0·10) [4]
Tooth extraction	2(0·07) [2]	0	2(0·05) [2]
Dental implantation	0	1(0·10) [1]	1(0·02) [1]
Wisdom teeth removal	1(0·03) [1]	0	1(0·02) [1]
Cardiac disorders	3(0·10) [3]	0	3(0·07) [3]
Palpitations	2(0·07) [2]	0	2(0·05) [2]
Acute myocardial infarction	1(0·03) [1]	0	1(0·02) [1]
Immune system disorders	2(0·07) [2]	0	2(0·05) [2]
Food allergy	1(0·03) [1]	0	1(0·02) [1]
Hypersensitivity	1(0·03) [1]	0	1(0·02) [1]
Reproductive system and breast disorders	1(0·03) [1]	1(0·10) [1]	2(0·05) [2]
Cervix inflammation	1(0·03) [1]	0	1(0·02) [1]
Vaginal haemorrhage	0	1(0·10) [1]	1(0·02) [1]
Hepatobiliary disorders	0	1(0·10) [2]	1(0·02) [2]
Cholangitis acute	0	1(0·10) [1]	1(0·02) [1]
Cholecystitis acute	0	1(0·10) [1]	1(0·02) [1]
Blood and lymphatic system disorders	1(0·03) [1]	0	1(0·02) [1]
Lymphadenopathy	1(0·03) [1]	0	1(0·02) [1]
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	0	1(0·10) [1]	1(0·02) [1]
Uterine leiomyoma	0	1(0·10) [1]	1(0·02) [1]
Psychiatric disorders	1(0·03) [1]	0	1(0·02) [1]
Schizophrenia	1(0·03) [1]	0	1(0·02) [1]
Vascular disorders	1(0·03) [1]	0	1(0·02) [1]
Hypertension	1(0·03) [1]	0	1(0·02) [1]

MAAEs = medically attended adverse events.
MedDRA version: 24.0
95% confidence interval was calculated by Clopper-Pearson Methods.
[1] Testing for between-treatment groups (chi-square test (c) or Fisher's exact test (f)).
Adverse events are displayed as 'number of participants (percentage of participants) [number of events]'. Denominator of percentage is the number of participants in each group. COVID-19 confirmed cases were diagnosed by the virological (PCR) test. COVID-19 cases diagnosed by the rapid antibody, and not confirmed via PCR, are considered suspected COVID-19 cases.

Table S27. Incidence of MAAEs by System Organ Class / Preferred Term Safety Set [6 months follow up]

System organ class Preferred term	GBP510 (N=3029)	ChAdOx1-S (N=996)	Total (N=4025)
Participants with MAAEs during 6-month follow-up period from 28 days after vaccination	210(6·93) [239]	70(7·03) [87]	280(6·96) [326]
95% Confidence Interval	[6·05, 7·90]	[5·52, 8·80]	[6·19, 7·79]
P-value [1]			0·92 (c)
Infections and infestations	165(5·45) [169]	54(5·42) [56]	219(5·44) [225]
COVID-19	76(2·51) [76]	29(2·91) [29]	105(2·61) [105]
Suspected COVID-19	64(2·11) [64]	14(1·41) [14]	78(1·94) [78]
Upper respiratory tract infection	6(0·20) [6]	1(0·10) [1]	7(0·17) [7]
Nasopharyngitis	1(0·03) [1]	2(0·20) [2]	3(0·07) [3]
Urinary tract infection	3(0·10) [3]	0	3(0·07) [3]
Cellulitis	0	2(0·20) [2]	2(0·05) [2]
Gastroenteritis	0	2(0·20) [2]	2(0·05) [2]
Gingivitis	0	2(0·20) [2]	2(0·05) [2]
Hordeolum	1(0·03) [1]	1(0·10) [1]	2(0·05) [2]
Abscess limb	1(0·03) [1]	0	1(0·02) [1]
Bartholin's abscess	1(0·03) [1]	0	1(0·02) [1]
Bronchitis	1(0·03) [1]	0	1(0·02) [1]
Conjunctivitis	1(0·03) [1]	0	1(0·02) [1]
Cystitis	1(0·03) [1]	0	1(0·02) [1]
Folliculitis	1(0·03) [1]	0	1(0·02) [1]
Herpes zoster	1(0·03) [1]	0	1(0·02) [1]
Laryngopharyngitis	1(0·03) [1]	0	1(0·02) [1]
Mycotic corneal ulcer	1(0·03) [1]	0	1(0·02) [1]
Otitis media	1(0·03) [1]	0	1(0·02) [1]
Periorbital cellulitis	1(0·03) [1]	0	1(0·02) [1]
Pharyngitis	1(0·03) [1]	0	1(0·02) [1]
Pneumonia	0	1(0·10) [1]	1(0·02) [1]
Pulpitis dental	1(0·03) [1]	0	1(0·02) [1]
Rhinitis	0	1(0·10) [1]	1(0·02) [1]
Scrub typhus	1(0·03) [1]	0	1(0·02) [1]
Sinusitis	1(0·03) [1]	0	1(0·02) [1]
Subcutaneous abscess	1(0·03) [1]	0	1(0·02) [1]
Tinea versicolour	1(0·03) [1]	0	1(0·02) [1]
Tonsillitis	1(0·03) [1]	0	1(0·02) [1]
Vaginal infection	0	1(0·10) [1]	1(0·02) [1]
Musculoskeletal and connective tissue disorders	8(0·26) [10]	4(0·40) [4]	12(0·30) [14]
Back pain	2(0·07) [3]	3(0·30) [3]	5(0·12) [6]
Myalgia	1(0·03) [2]	1(0·10) [1]	2(0·05) [3]
Intervertebral disc protrusion	2(0·07) [2]	0	2(0·05) [2]
Arthralgia	1(0·03) [1]	0	1(0·02) [1]
Intervertebral disc degeneration	1(0·03) [1]	0	1(0·02) [1]
Periarthritis	1(0·03) [1]	0	1(0·02) [1]
Gastrointestinal disorders	5(0·17) [5]	6(0·60) [7]	11(0·27) [12]
Gastrooesophageal reflux disease	2(0·07) [2]	1(0·10) [1]	3(0·07) [3]
Abdominal pain	1(0·03) [1]	1(0·10) [1]	2(0·05) [2]
Abdominal pain upper	0	1(0·10) [1]	1(0·02) [1]
Dyspepsia	0	1(0·10) [1]	1(0·02) [1]
Gastric ulcer	1(0·03) [1]	0	1(0·02) [1]

System organ class Preferred term	GBP510 (N=3029)	ChAdOx1-S (N=996)	Total (N=4025)
Gastritis	0	1(0·10) [1]	1(0·02) [1]
Haemorrhoids	1(0·03) [1]	0	1(0·02) [1]
Periodontal disease	0	1(0·10) [1]	1(0·02) [1]
Toothache	0	1(0·10) [1]	1(0·02) [1]
Injury, poisoning and procedural complications	8(0·26) [8]	3(0·30) [3]	11(0·27) [11]
Burns first degree	1(0·03) [1]	0	1(0·02) [1]
Clavicle fracture	0	1(0·10) [1]	1(0·02) [1]
Contusion	1(0·03) [1]	0	1(0·02) [1]
Foreign body in throat	1(0·03) [1]	0	1(0·02) [1]
Ligament sprain	0	1(0·10) [1]	1(0·02) [1]
Limb injury	1(0·03) [1]	0	1(0·02) [1]
Multiple injuries	0	1(0·10) [1]	1(0·02) [1]
Postpolypectomy syndrome	1(0·03) [1]	0	1(0·02) [1]
Skin abrasion	1(0·03) [1]	0	1(0·02) [1]
Skin laceration	1(0·03) [1]	0	1(0·02) [1]
Wrist fracture	1(0·03) [1]	0	1(0·02) [1]
Skin and subcutaneous tissue disorders	7(0·23) [9]	2(0·20) [2]	9(0·22) [11]
Urticaria	1(0·03) [1]	1(0·10) [1]	2(0·05) [2]
Rash	1(0·03) [2]	0	1(0·02) [2]
Acne	1(0·03) [1]	0	1(0·02) [1]
Cold urticaria	1(0·03) [1]	0	1(0·02) [1]
Cutaneous vasculitis	1(0·03) [1]	0	1(0·02) [1]
Diffuse alopecia	1(0·03) [1]	0	1(0·02) [1]
Neurodermatitis	1(0·03) [1]	0	1(0·02) [1]
Prurigo	1(0·03) [1]	0	1(0·02) [1]
Psoriasis	0	1(0·10) [1]	1(0·02) [1]
Nervous system disorders	6(0·20) [6]	3(0·30) [3]	9(0·22) [9]
Headache	2(0·07) [2]	1(0·10) [1]	3(0·07) [3]
Cerebral infarction	1(0·03) [1]	0	1(0·02) [1]
Dizziness	1(0·03) [1]	0	1(0·02) [1]
Haemorrhage intracranial	1(0·03) [1]	0	1(0·02) [1]
Paraesthesia	1(0·03) [1]	0	1(0·02) [1]
Syncope	0	1(0·10) [1]	1(0·02) [1]
Trigeminal neuralgia	0	1(0·10) [1]	1(0·02) [1]
Respiratory, thoracic and mediastinal disorders	7(0·23) [7]	0	7(0·17) [7]
Cough	3(0·10) [3]	0	3(0·07) [3]
Rhinitis allergic	2(0·07) [2]	0	2(0·05) [2]
Allergic cough	1(0·03) [1]	0	1(0·02) [1]
Bronchitis chronic	1(0·03) [1]	0	1(0·02) [1]
Vascular disorders	6(0·20) [6]	1(0·10) [1]	7(0·17) [7]
Hypertension	6(0·20) [6]	1(0·10) [1]	7(0·17) [7]
General disorders and administration site conditions	5(0·17) [5]	0	5(0·12) [5]
Chest pain	2(0·07) [2]	0	2(0·05) [2]
Inflammation	1(0·03) [1]	0	1(0·02) [1]
Pain	1(0·03) [1]	0	1(0·02) [1]
Soft tissue inflammation	1(0·03) [1]	0	1(0·02) [1]
Psychiatric disorders	4(0·13) [4]	0	4(0·10) [4]
Insomnia	2(0·07) [2]	0	2(0·05) [2]
Anxiety	1(0·03) [1]	0	1(0·02) [1]
Depression	1(0·03) [1]	0	1(0·02) [1]
Hepatobiliary disorders	0	3(0·30) [4]	3(0·07) [4]

System organ class Preferred term	GBP510 (N=3029)	ChAdOx1-S (N=996)	Total (N=4025)
Cholangitis acute	0	1(0·10) [1]	1(0·02) [1]
Cholecystitis acute	0	1(0·10) [1]	1(0·02) [1]
Cholelithiasis	0	1(0·10) [1]	1(0·02) [1]
Hepatic steatosis	0	1(0·10) [1]	1(0·02) [1]
Metabolism and nutrition disorders	1(0·03) [1]	2(0·20) [2]	3(0·07) [3]
Dyslipidaemia	1(0·03) [1]	0	1(0·02) [1]
Hyperlipidaemia	0	1(0·10) [1]	1(0·02) [1]
Vitamin D deficiency	0	1(0·10) [1]	1(0·02) [1]
Immune system disorders	1(0·03) [1]	1(0·10) [1]	2(0·05) [2]
Anaphylactic reaction	0	1(0·10) [1]	1(0·02) [1]
Drug hypersensitivity	1(0·03) [1]	0	1(0·02) [1]
Investigations	0	1(0·10) [2]	1(0·02) [2]
Blood glucose increased	0	1(0·10) [2]	1(0·02) [2]
Blood and lymphatic system disorders	1(0·03) [1]	0	1(0·02) [1]
Anaemia	1(0·03) [1]	0	1(0·02) [1]
Cardiac disorders	1(0·03) [1]	0	1(0·02) [1]
Myocardial ischaemia	1(0·03) [1]	0	1(0·02) [1]
Congenital, familial and genetic disorders	1(0·03) [1]	0	1(0·02) [1]
Foetal malformation	1(0·03) [1]	0	1(0·02) [1]
Ear and labyrinth disorders	1(0·03) [1]	0	1(0·02) [1]
Tinnitus	1(0·03) [1]	0	1(0·02) [1]
Endocrine disorders	1(0·03) [1]	0	1(0·02) [1]
Hypothyroidism	1(0·03) [1]	0	1(0·02) [1]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1(0·03) [1]	0	1(0·02) [1]
Brain neoplasm	1(0·03) [1]	0	1(0·02) [1]
Pregnancy, puerperium and perinatal conditions	0	1(0·10) [1]	1(0·02) [1]
Abortion missed	0	1(0·10) [1]	1(0·02) [1]
Renal and urinary disorders	0	1(0·10) [1]	1(0·02) [1]
Tubulointerstitial nephritis	0	1(0·10) [1]	1(0·02) [1]
Reproductive system and breast disorders	1(0·03) [1]	0	1(0·02) [1]
Menstrual disorder	1(0·03) [1]	0	1(0·02) [1]
Surgical and medical procedures	1(0·03) [1]	0	1(0·02) [1]
Tooth extraction	1(0·03) [1]	0	1(0·02) [1]

MAAEs = medically attended adverse events.
MedDRA version: 24·0
95% confidence interval was calculated by Clopper-Pearson Methods.
[1] Testing for between-treatment groups (chi-square test (c) or Fisher's exact test (f)).
Adverse events are displayed as 'number of participants (percentage of participants) [number of events]'. Denominator of percentage is the number of participants in each group. COVID-19 confirmed cases were diagnosed by the virological (PCR) test. COVID-19 cases diagnosed by the rapid antibody, and not confirmed via PCR, are considered suspected COVID-19 cases.

Table S28. Incidence of AESIs by System Organ Class / Preferred Term Safety Set [up to 4 weeks after 2nd vaccination]

System organ class Preferred term	GBP510 (N=3029)	ChAdOx1-S (N=996)	Total (N=4025)
Participants with AESIs	2(0·07) [2]	1(0·10) [1]	3(0·07) [3]
Exact 95% Confidence Interval	[0·01, 0·24]	[0·00, 0·56]	[0·02, 0·22]
P-value [1]			0·57 (f)
Renal and urinary disorders	2(0·07) [2]	0	2(0·05) [2]
Acute kidney injury	1(0·03) [1]	0	1(0·02) [1]
Glomerulonephritis rapidly progressive	1(0·03) [1]	0	1(0·02) [1]
Gastrointestinal disorders	0	1(0·10) [1]	1(0·02) [1]
Pancreatitis acute	0	1(0·10) [1]	1(0·02) [1]

AESIs = adverse events of special interest.
MedDRA version: 24·0
95% confidence interval was calculated by Clopper-Pearson Methods.
[1] Testing for between-treatment groups (chi-square test (c) or Fisher's exact test (f)).
Adverse events are displayed as 'number of participants (percentage of participants) [number of events]'. Denominator of percentage is the number of participants in each group.

Table S29. Incidence of AESIs by System Organ Class / Preferred Term Safety Set [6 months follow up]

System organ class Preferred term	GBP510 (N=3029)	ChAdOx1-S (N=996)	Total (N=4025)
Participants with AESIs during 6-month follow-up period from 28 days after vaccination	1(0·03) [1]	2(0·20) [2]	3(0·07) [3]
95% Confidence Interval	[0·00, 0·18]	[0·02, 0·72]	[0·02, 0·22]
P-value [1]			0·15 (f)
Skin and subcutaneous tissue disorders	1(0·03) [1]	1(0·10) [1]	2(0·05) [2]
Cutaneous vasculitis	1(0·03) [1]	0	1(0·02) [1]
Psoriasis	0	1(0·10) [1]	1(0·02) [1]
Immune system disorders	0	1(0·10) [1]	1(0·02) [1]
Anaphylactic reaction	0	1(0·10) [1]	1(0·02) [1]

AESIs = adverse events of special interest.
MedDRA version: 24·0
95% confidence interval was calculated by Clopper-Pearson Methods.
[1] Testing for between-treatment groups (chi-square test (c) or Fisher's exact test (f)).
Adverse events are displayed as 'number of participants (percentage of participants) [number of events]'. Denominator of percentage is the number of participants in each group.

Table S30. Serious Adverse Events by System Organ Class / Preferred Term Safety Set [up to 4 weeks after 2nd vaccination]

System organ class Preferred term	GBP510 (N=3029)	ChAdOx1-S (N=996)	Total (N=4025)
Participants with Serious Adverse Events	15(0·50) [15]	7(0·70) [9]	22(0·55) [24]
Exact 95% Confidence Interval	[0·28, 0·82]	[0·28, 1·44]	[0·34, 0·83]
P-value [1]			0·44 (c)
Serious Solicited Local AEs			
Injection Site Pain	0	0	0
Injection Site Redness	0	0	0
Injection Site Swelling	0	0	0
Serious Solicited Systemic AEs			
Fever	0	0	0
Nausea/Vomiting	0	0	0
Diarrhea	0	0	0
Headache	0	0	0
Fatigue	0	0	0
Myalgia	0	0	0
Arthralgia	0	0	0
Chills	0	0	0
Serious Unsolicited Adverse Events			
Infections and infestations	8(0·26) [8]	4(0·40) [4]	12(0·30) [12]
COVID-19	5(0·17) [5]	4(0·40) [4]	9(0·22) [9]
Anal abscess	1(0·03) [1]	0	1(0·02) [1]
Appendicitis	1(0·03) [1]	0	1(0·02) [1]
Pneumonia	1(0·03) [1]	0	1(0·02) [1]
Gastrointestinal disorders	1(0·03) [1]	1(0·10) [2]	2(0·05) [3]
Gastrooesophageal reflux disease	1(0·03) [1]	1(0·10) [1]	2(0·05) [2]
Pancreatitis acute	0	1(0·10) [1]	1(0·02) [1]
Cardiac disorders	1(0·03) [1]	1(0·10) [1]	2(0·05) [2]
Acute myocardial infarction	1(0·03) [1]	0	1(0·02) [1]
Cardiopulmonary failure	0	1(0·10) [1]	1(0·02) [1]
Injury, poisoning and procedural complications	2(0·07) [2]	0	2(0·05) [2]
Hand fracture	1(0·03) [1]	0	1(0·02) [1]
Skin laceration	1(0·03) [1]	0	1(0·02) [1]
Hepatobiliary disorders	0	1(0·10) [2]	1(0·02) [2]
Cholangitis acute	0	1(0·10) [1]	1(0·02) [1]
Cholecystitis acute	0	1(0·10) [1]	1(0·02) [1]
Musculoskeletal and connective tissue disorders	1(0·03) [1]	0	1(0·02) [1]
Rotator cuff syndrome	1(0·03) [1]	0	1(0·02) [1]
Psychiatric disorders	1(0·03) [1]	0	1(0·02) [1]

System organ class Preferred term	GBP510 (N=3029)	ChAdOx1-S (N=996)	Total (N=4025)
Schizophrenia	1(0·03) [1]	0	1(0·02) [1]
Renal and urinary disorders	1(0·03) [1]	0	1(0·02) [1]
Glomerulonephritis rapidly progressive	1(0·03) [1]	0	1(0·02) [1]

AEs = adverse events.
MedDRA version: 24·0.
[1] Testing for between-treatment groups (chi-square test (c) or Fisher's exact test (f)).
Adverse events are displayed as 'number of participants (percentage of participants) [number of events]'. Denominator of percentage is the number of participants in each group. COVID-19 confirmed cases were diagnosed by the virological (PCR) test. COVID-19 cases diagnosed by the rapid antibody, and not confirmed via PCR, are considered suspected COVID-19 cases.

Table S31. Serious Adverse Events by System Organ Class / Preferred Term Safety Set [6 months follow up]

System organ class Preferred term	GBP510 (N=3029)	ChAdOx1-S (N=996)	Total (N=4025)
Participants with Serious Adverse Events during 6-month follow-up period from 28 days after vaccination	16(0·53) [17]	5(0·50) [7]	21(0·52) [24]
95% Confidence Interval	[0·30, 0·86]	[0·16, 1·17]	[0·32, 0·80]
P-value [1]			0·92 (c)
Infections and infestations	9(0·30) [10]	0	9(0·22) [10]
COVID-19	7(0·23) [7]	0	7(0·17) [7]
Bartholin's abscess	1(0·03) [1]	0	1(0·02) [1]
Scrub typhus	1(0·03) [1]	0	1(0·02) [1]
Suspected COVID-19	1(0·03) [1]	0	1(0·02) [1]
Hepatobiliary disorders	0	2(0·20) [3]	2(0·05) [3]
Cholangitis acute	0	1(0·10) [1]	1(0·02) [1]
Cholecystitis acute	0	1(0·10) [1]	1(0·02) [1]
Cholelithiasis	0	1(0·10) [1]	1(0·02) [1]
Injury, poisoning and procedural complications	1(0·03) [1]	1(0·10) [1]	2(0·05) [2]
Multiple injuries	0	1(0·10) [1]	1(0·02) [1]
Postpolypectomy syndrome	1(0·03) [1]	0	1(0·02) [1]
Nervous system disorders	2(0·07) [2]	0	2(0·05) [2]
Cerebral infarction	1(0·03) [1]	0	1(0·02) [1]
Haemorrhage intracranial	1(0·03) [1]	0	1(0·02) [1]
Congenital, familial and genetic disorders	1(0·03) [1]	0	1(0·02) [1]
Foetal malformation	1(0·03) [1]	0	1(0·02) [1]
General disorders and administration site conditions	1(0·03) [1]	0	1(0·02) [1]
Chest pain	1(0·03) [1]	0	1(0·02) [1]
Investigations	0	1(0·10) [1]	1(0·02) [1]
Blood glucose increased	0	1(0·10) [1]	1(0·02) [1]
Musculoskeletal and connective tissue disorders	1(0·03) [1]	0	1(0·02) [1]
Back pain	1(0·03) [1]	0	1(0·02) [1]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1(0·03) [1]	0	1(0·02) [1]
Brain neoplasm	1(0·03) [1]	0	1(0·02) [1]
Pregnancy, puerperium and perinatal conditions	0	1(0·10) [1]	1(0·02) [1]
Abortion missed	0	1(0·10) [1]	1(0·02) [1]
Renal and urinary disorders	0	1(0·10) [1]	1(0·02) [1]
Tubulointerstitial nephritis	0	1(0·10) [1]	1(0·02) [1]

AEs = adverse events.
MedDRA version: 24·0.
95% confidence interval was calculated by Clopper-Pearson Methods.
[1] Testing for between-treatment groups (chi-square test (c) or Fisher's exact test (f)).
Adverse events are displayed as 'number of participants (percentage of participants) [number of events]'. Denominator of percentage is the number of participants in each group. COVID-19 confirmed cases were diagnosed by the virological (PCR) test. COVID-19 cases diagnosed by the rapid antibody, and not confirmed via PCR, are considered suspected COVID-19 cases.

Table S32. The Incidence Rates of Virologically-confirmed or suspected COVID-19 Safety Set [6 months follow up]

	GBP510 (N=3029)	ChAdOx1-S (N=996)
During 6-month follow-up period after any vaccination	338(11·16) [340]	116(11·65) [116]
95% Confidence Interval	[10·06, 12·33]	[9·72, 13·80]
P-value [1]	0·67 (c)	
Severity		
Asymptomatic	76(2·51) [76]	28(2·81) [28]
Non-severe	262(8·65) [264]	88(8·84) [88]
Severe	0	0
Critical	0	0
<14 days after 1st vaccination	9(0·30) [9]	1(0·10) [1]
95% Confidence Interval	[0·14, 0·56]	[0·00, 0·56]
P-value [1]	0·47 (f)	
Severity		
Asymptomatic	3(0·10) [3]	0
Non-severe	6(0·20) [6]	1(0·10) [1]
Severe	0	0
Critical	0	0
≥ 14 days after 1st vaccination and before 2nd vaccination	68(2·24) [68]	19(1·91) [19]
95% Confidence Interval	[1·75, 2·84]	[1·15, 2·96]
P-value [1]	0·53 (c)	
Severity		
Asymptomatic	43(1·42) [43]	12(1·20) [12]
Non-severe	25(0·83) [25]	7(0·70) [7]
Severe	0	0
Critical	0	0
After 2nd vaccination and <14 days after 2nd vaccination	7(0·23) [7]	2(0·20) [2]
95% Confidence Interval	[0·09, 0·48]	[0·02, 0·72]
P-value [1]	1·00 (f)	
Severity		
Asymptomatic	3(0·10) [3]	0
Non-severe	4(0·13) [4]	2(0·20) [2]
Severe	0	0
Critical	0	0
≥ 14 days after 2nd vaccination	254(8·39) [256]	94(9·44) [94]
95% Confidence Interval	[7·42, 9·43]	[7·69, 11·43]
P-value [1]	0·31 (c)	
Severity		
Asymptomatic	27(0·89) [27]	16(1·61) [16]
Non-severe	227(7·49) [229]	78(7·83) [78]
Severe	0	0

	GBP510 (N=3029)	ChAdOx1-S (N=996)
Critical	0	0

[1] Testing for between-treatment groups (chi-square test (c) or Fisher's exact test (f)).Data are presented as 'number of participants (% participants) [number of events]'. Denominator of percentage is the number of participants in each group. 95% confidence interval was calculated by Clopper-Pearson Methods.

Table S33. Comorbidities with Higher risk for severe COVID-19 in all participants at baseline (Intention-to-Treat Set)

	GBP510 (N=3,039)	ChAdOx1-S (N=997)	Total (N=4,036)
Participants with Comorbidity	**539(17·74) [708]**	**212(21·26) [287]**	**751(18·61) [995]**
BMI>30 kg/m^2	245(8·06) [245]	84(8·43) [84]	329(8·15) [329]
Hypertension	188(6·19) [188]	100(10·03) [100]	288(7·14) [288]
Age≥65 years	161(5·30) [161]	54(5·42) [54]	215(5·33) [215]
Diabetes mellitus*	26(0·86) [26]	14(1·40) [14]	40(0·99) [40]
Asthma	17(0·56) [17]	5(0·50) [5]	22(0·55) [22]
Type 2 diabetes mellitus	15(0·49) [15]	5(0·50) [5]	20(0·50) [20]
Myocardial ischaemia	11(0·36) [11]	6(0·60) [6]	17(0·42) [17]
Cardiac failure chronic	6(0·20) [6]	4(0·40) [4]	10(0·25) [10]
HIV infection	7(0·23) [7]	2(0·20) [2]	9(0·22) [9]
Depression	4(0·13) [4]	2(0·20) [2]	6(0·15) [6]
Atrial fibrillation	4(0·13) [4]	0(0·00) [0]	4(0·10) [4]
Myocardial fibrosis	1(0·03) [1]	3(0·30) [3]	4(0·10) [4]
Angina pectoris	2(0·07) [2]	1(0·10) [1]	3(0·07) [3]
Hepatic steatosis	3(0·10) [3]	0(0·00) [0]	3(0·07) [3]
Cerebral infarction	0(0·00) [0]	2(0·20) [2]	2(0·05) [2]
Cerebrovascular disorder	0(0·00) [0]	2(0·20) [2]	2(0·05) [2]
Nephrolithiasis	2(0·07) [2]	0(0·00) [0]	2(0·05) [2]
Acute coronary syndrome	1(0·03) [1]	0(0·00) [0]	1(0·02) [1]
Aortic valve stenosis	1(0·03) [1]	0(0·00) [0]	1(0·02) [1]
Brief psychotic disorder without marked stressors	0(0·00) [0]	1(0·10) [1]	1(0·02) [1]
Cardiac valve disease	1(0·03) [1]	0(0·00) [0]	1(0·02) [1]
Cerebral artery stenosis	1(0·03) [1]	0(0·00) [0]	1(0·02) [1]
Cerebrovascular accident	0(0·00) [0]	1(0·10) [1]	1(0·02) [1]
Chronic obstructive pulmonary disease	1(0·03) [1]	0(0·00) [0]	1(0·02) [1]
Coronary artery disease	1(0·03) [1]	0(0·00) [0]	1(0·02) [1]
Hypertensive heart disease	1(0·03) [1]	0(0·00) [0]	1(0·02) [1]
Ischaemic cardiomyopathy	1(0·03) [1]	0(0·00) [0]	1(0·02) [1]
Ischaemic stroke	1(0·03) [1]	0(0·00) [0]	1(0·02) [1]
Left ventricular failure	1(0·03) [1]	0(0·00) [0]	1(0·02) [1]
Mental disorder	0(0·00) [0]	1(0·10) [1]	1(0·02) [1]
Myocardial infarction	1(0·03) [1]	0(0·00) [0]	1(0·02) [1]
Prostate cancer	1(0·03) [1]	0(0·00) [0]	1(0·02) [1]
Pyelonephritis chronic	1(0·03) [1]	0(0·00) [0]	1(0·02) [1]
Sinus tachycardia	1(0·03) [1]	0(0·00) [0]	1(0·02) [1]
Tachycardia	1(0·03) [1]	0(0·00) [0]	1(0·02) [1]
Transient ischaemic attack	1(0·03) [1]	0(0·00) [0]	1(0·02) [1]

MedDRA version 24.0.

Comorbidities are displayed as 'number of participants (percentage of participants) [number of event]'. Denominator of percentage is the number of participants in each group.

* Diabetes type not reported

The definition of the high-risk group is based on the "Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19 'released by the US CDC (Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Professionals | CDC

Table S34. Overall Adverse Events Safety Set [Subgroup: Race: Asian (Korean)]: up to 4 weeks after 2nd vaccination

	GBP510 (N=327)	ChAdOx1-S (N=168)	Total (N=495)
Adverse Events after any vaccine injection			
Participants with Immediate Unsolicited AEs	1(0·31) [1]	0	1(0·20) [1]
Exact 95% Confidence Interval	[0·01, 1·69]	[0·00, 2·17]	[0·01, 1·12]
Participants with Immediate Unsolicited ADRs	1(0·31) [1]	0	1(0·20) [1]
Exact 95% Confidence Interval	[0·01, 1·69]	[0·00, 2·17]	[0·01, 1·12]
Solicited reaction within 7 days after vaccination			
Participants with Solicited Local AEs	317(96·94) [712]	143(85·12) [223]	460(92·93) [935]
Exact 95% Confidence Interval	[94·45, 98·52]	[78·82, 90·13]	[90·30, 95·03]
Participants with Solicited Systemic AEs	306(93·58) [1651]	156(92·86) [779]	462(93·33) [2430]
Exact 95% Confidence Interval	[90·35, 95·98]	[87·86, 96·25]	[90·76, 95·37]
Within 28 days after vaccination			
Participants with Unsolicited AEs	123(37·61) [267]	51(30·36) [96]	174(35·15) [363]
Exact 95% Confidence Interval	[32·34, 43·11]	[23·51, 37·91]	[30·94, 39·54]
Participants with Unsolicited ADRs	55(16·82) [97]	24(14·29) [39]	79(15·96) [136]
Exact 95% Confidence Interval	[12·93, 21·32]	[9·37, 20·51]	[12·84, 19·49]
Participants with SAEs	5(1·53) [5]	0	5(1·01) [5]
Exact 95% Confidence Interval	[0·50, 3·53]	[0·00, 2·17]	[0·33, 2·34]
Participants with AESIs	0	0	0
Exact 95% Confidence Interval	[0·00, 1·12]	[0·00, 2·17]	[0·00, 0·74]
Participants with MAAEs	47(14·37) [63]	24(14·29) [35]	71(14·34) [98]
Exact 95% Confidence Interval	[10·76, 18·65]	[9·37, 20·51]	[11·38, 17·75]
Participants with MAADRs	9(2·75) [12]	6(3·57) [11]	15(3·03) [23]
Exact 95% Confidence Interval	[1·27, 5·16]	[1·32, 7·61]	[1·71, 4·95]
Participants with AEs leading to study withdrawal*	0	0	0
Exact 95% Confidence Interval	[0·00, 1·12]	[0·00, 2·17]	[0·00, 0·74]
Participants with AEs leading to death**	0	0	0
Exact 95% Confidence Interval	[0·00, 1·12]	[0·00, 2·17]	[0·00, 0·74]

AEs = adverse events, ADRs= adverse drug reactions, MAAEs = medically attended adverse events, SAEs = serious adverse events, SADRs = serious adverse drug reactions, AESIs = adverse events of special interest.

Data are presented as 'number of participants (% participants) [number of events]'. Denominator of percentage is the number of participants in each group. 95% confidence interval was calculated by Clopper-Pearson Methods.

* The case checked on 'at the discretion of the investigator or sponsor due to safety concerns' as a primary reason for discontinuation and checked on 'Stop Vaccination (only if, prior to 2nd vaccination)' as changes to IP vaccination.

** The case checked on 'Death' as a primary reason for discontinuation and checked on 'Fatal' as outcome.

Table S35. Overall Adverse Events Safety Set [Subgroup: Race: Asian (Southeast Asian)]: up to 4 weeks after 2nd vaccination

	GBP510 (N=2521)	ChAdOx1-S (N=761)	Total (N=3282)
Adverse Events after any vaccine injection			
Participants with Immediate Unsolicited AEs	1(0·04) [1]	0	1(0·03) [1]
Exact 95% Confidence Interval	[0·00, 0·22]	[0·00, 0·48]	[0·00, 0·17]
Participants with Immediate Unsolicited ADRs	1(0·04) [1]	0	1(0·03) [1]
Exact 95% Confidence Interval	[0·00, 0·22]	[0·00, 0·48]	[0·00, 0·17]
Solicited reaction within 7 days after vaccination			
Participants with Solicited Local AEs	1258(49·90) [1950]	302(39·68) [383]	1560(47·53) [2333]
Exact 95% Confidence Interval	[47·93, 51·87]	[36·19, 43·26]	[45·81, 49·26]
Participants with Solicited Systemic AEs	1108(43·95) [3858]	333(43·76) [1092]	1441(43·91) [4950]
Exact 95% Confidence Interval	[42·00, 45·91]	[40·20, 47·37]	[42·20, 45·62]
Within 28 days after vaccination			
Participants with Unsolicited AEs	210(8·33) [255]	73(9·59) [84]	283(8·62) [339]
Exact 95% Confidence Interval	[7·28, 9·48]	[7·59, 11·91]	[7·68, 9·64]
Participants with Unsolicited ADRs	22(0·87) [23]	6(0·79) [6]	28(0·85) [29]
Exact 95% Confidence Interval	[0·55, 1·32]	[0·29, 1·71]	[0·57, 1·23]
Participants with SAEs	9(0·36) [9]	7(0·92) [9]	16(0·49) [18]
Exact 95% Confidence Interval	[0·16, 0·68]	[0·37, 1·89]	[0·28, 0·79]
Participants with AESIs	2(0·08) [2]	1(0·13) [1]	3(0·09) [3]
Exact 95% Confidence Interval	[0·01, 0·29]	[0·00, 0·73]	[0·02, 0·27]
Participants with MAAEs	82(3·25) [85]	21(2·76) [25]	103(3·14) [110]
Exact 95% Confidence Interval	[2·60, 4·02]	[1·72, 4·19]	[2·57, 3·79]
Participants with MAADRs	2(0·08) [2]	1(0·13) [1]	3(0·09) [3]
Exact 95% Confidence Interval	[0·01, 0·29]	[0·00, 0·73]	[0·02, 0·27]
Participants with AEs leading to study withdrawal*	3(0·12) [8]	2(0·26) [3]	5(0·15) [11]
Exact 95% Confidence Interval	[0·02, 0·35]	[0·03, 0·95]	[0·05, 0·36]
Participants with AEs leading to death**	0	1(0·13) [1]	1(0·03) [1]
Exact 95% Confidence Interval	[0·00, 0·15]	[0·00, 0·73]	[0·00, 0·17]

AEs = adverse events, ADRs= adverse drug reactions, MAAEs = medically attended adverse events, SAEs = serious adverse events, SADRs = serious adverse drug reactions, AESIs = adverse events of special interest.

Data are presented as 'number of participants (% participants) [number of events]'. Denominator of percentage is the number of participants in each group. 95% confidence interval was calculated by Clopper-Pearson Methods.

* The case checked on 'at the discretion of the investigator or sponsor due to safety concerns' as a primary reason for discontinuation and checked on 'Stop Vaccination (only if, prior to 2nd vaccination)' as changes to IP vaccination.

** The case checked on 'Death' as a primary reason for discontinuation and checked on 'Fatal' as outcome.

Table S36. Overall Adverse Events Safety Set [Subgroup: Race: Asian (Caucasian)]: up to 4 weeks after 2nd vaccination

	GBP510 (N=174)	ChAdOx1-S (N=64)	Total (N=238)
Adverse Events after any vaccine injection			
Participants with Immediate Unsolicited AEs	4(2·30) [5]	0	4(1·68) [5]
Exact 95% Confidence Interval	[0·63, 5·78]	[0·00, 5·60]	[0·46, 4·25]
Participants with Immediate Unsolicited ADRs	3(1·72) [4]	0	3(1·26) [4]
Exact 95% Confidence Interval	[0·36, 4·96]	[0·00, 5·60]	[0·26, 3·64]
Solicited reaction within 7 days after vaccination			
Participants with Solicited Local AEs	136(78·16) [273]	42(65·63) [63]	178(74·79) [336]
Exact 95% Confidence Interval	[71·28, 84·06]	[52·70, 77·05]	[68·77, 80·18]
Participants with Solicited Systemic AEs	130(74·71) [582]	42(65·63) [176]	172(72·27) [758]
Exact 95% Confidence Interval	[67·58, 80·99]	[52·70, 77·05]	[66·12, 77·86]
Within 28 days after vaccination			
Participants with Unsolicited AEs	65(37·36) [110]	18(28·13) [29]	83(34·87) [139]
Exact 95% Confidence Interval	[30·15, 45·00]	[17·60, 40·76]	[28·83, 41·30]
Participants with Unsolicited ADRs	28(16·09) [43]	9(14·06) [12]	37(15·55) [55]
Exact 95% Confidence Interval	[10·97, 22·41]	[6·64, 25·02]	[11·19, 20·79]
Participants with SAEs	1(0·57) [1]	0	1(0·42) [1]
Exact 95% Confidence Interval	[0·01, 3·16]	[0·00, 5·60]	[0·01, 2·32]
Participants with AESIs	0	0	0
Exact 95% Confidence Interval	[0·00, 2·10]	[0·00, 5·60]	[0·00, 1·54]
Participants with MAAEs	17(9·77) [22]	5(7·81) [9]	22(9·24) [31]
Exact 95% Confidence Interval	[5·80, 15·18]	[2·59, 17·30]	[5·88, 13·66]
Participants with MAADRs	6(3·45) [11]	3(4·69) [6]	9(3·78) [17]
Exact 95% Confidence Interval	[1·28, 7·35]	[0·98, 13·09]	[1·74, 7·06]
Participants with AEs leading to study withdrawal*	0	0	0
Exact 95% Confidence Interval	[0·00, 2·10]	[0·00, 5·60]	[0·00, 1·54]
Participants with AEs leading to death**	0	0	0
Exact 95% Confidence Interval	[0·00, 2·10]	[0·00, 5·60]	[0·00, 1·54]

AEs = adverse events, ADRs= adverse drug reactions, MAAEs = medically attended adverse events, SAEs = serious adverse events, SADRs = serious adverse drug reactions, AESIs = adverse events of special interest.

Data are presented as 'number of participants (% participants) [number of events]'. Denominator of percentage is the number of participants in each group. 95% confidence interval was calculated by Clopper-Pearson Methods.

* The case checked on 'at the discretion of the investigator or sponsor due to safety concerns' as a primary reason for discontinuation and checked on 'Stop Vaccination (only if, prior to 2nd vaccination)' as changes to IP vaccination.

** The case checked on 'Death' as a primary reason for discontinuation and checked on 'Fatal' as outcome.

Table S37. Unsolicited AE by System Organ Class / Preferred Term (Safety Set) [Up to 4 weeks after 2nd vaccination]

System organ class Preferred term	GBP510 (N=3029)	ChAdOx1-S (N=996)	Total (N=4025)
Participants with Unsolicited AEs	402(13·27) [640]	145(14·56) [213]	547(13·59) [853]
Exact 95% Confidence Interval	[12·08, 14·53]	[12·43, 16·90]	[12·55, 14·69]
P-value [1]			0·30 (c)
Infections and infestations	179(5·91) [189]	59(5·92) [60]	238(5·91) [249]
COVID-19	62(2·05) [62]	33(3·31) [33]	95(2·36) [95]
Suspected COVID-19	48(1·58) [48]	11(1·10) [11]	59(1·47) [59]
Upper respiratory tract infection	18(0·59) [18]	3(0·30) [3]	21(0·52) [21]
Nasopharyngitis	11(0·36) [12]	4(0·40) [4]	15(0·37) [16]
Rhinitis	7(0·23) [8]	2(0·20) [2]	9(0·22) [10]
Systemic viral infection	7(0·23) [7]	0	7(0·17) [7]
Tonsillitis	2(0·07) [2]	3(0·30) [3]	5(0·12) [5]
Herpes virus infection	2(0·07) [2]	1(0·10) [1]	3(0·07) [3]
Viral infection	3(0·10) [3]	0	3(0·07) [3]
Influenza	1(0·03) [2]	1(0·10) [1]	2(0·05) [3]
Conjunctivitis	2(0·07) [2]	0	2(0·05) [2]
Furuncle	2(0·07) [2]	0	2(0·05) [2]
Gastroenteritis	2(0·07) [2]	0	2(0·05) [2]
Hordeolum	2(0·07) [2]	0	2(0·05) [2]
Urinary tract infection	2(0·07) [2]	0	2(0·05) [2]
Anal abscess	1(0·03) [1]	0	1(0·02) [1]
Appendicitis	1(0·03) [1]	0	1(0·02) [1]
Bacterial vaginosis	1(0·03) [1]	0	1(0·02) [1]
Cystitis	0	1(0·10) [1]	1(0·02) [1]
Folliculitis	1(0·03) [1]	0	1(0·02) [1]
Laryngopharyngitis	1(0·03) [1]	0	1(0·02) [1]
Latent tuberculosis	1(0·03) [1]	0	1(0·02) [1]
Localised infection	1(0·03) [1]	0	1(0·02) [1]
Lower respiratory tract infection	1(0·03) [1]	0	1(0·02) [1]
Nail infection	1(0·03) [1]	0	1(0·02) [1]

System organ class Preferred term	GBP510 (N=3029)	ChAdOx1-S (N=996)	Total (N=4025)
Oral herpes	1(0·03) [1]	0	1(0·02) [1]
Otitis externa	0	1(0·10) [1]	1(0·02) [1]
Peritonsillitis	1(0·03) [1]	0	1(0·02) [1]
Pharyngitis	1(0·03) [1]	0	1(0·02) [1]
Pneumonia	1(0·03) [1]	0	1(0·02) [1]
Tinea pedis	1(0·03) [1]	0	1(0·02) [1]
Vaginal infection	1(0·03) [1]	0	1(0·02) [1]
Nervous system disorders	56(1·85) [68]	25(2·51) [29]	81(2·01) [97]
Dizziness	17(0·56) [19]	11(1·10) [11]	28(0·70) [30]
Headache	19(0·63) [24]	8(0·80) [8]	27(0·67) [32]
Hypoesthesia	3(0·10) [4]	3(0·30) [3]	6(0·15) [7]
Paraesthesia	5(0·17) [6]	1(0·10) [1]	6(0·15) [7]
Somnolence	4(0·13) [4]	2(0·20) [3]	6(0·15) [7]
Hypogeusia	1(0·03) [1]	1(0·10) [1]	2(0·05) [2]
Paralysis	2(0·07) [2]	0	2(0·05) [2]
Syncope	2(0·07) [2]	0	2(0·05) [2]
Dysgeusia	0	1(0·10) [2]	1(0·02) [2]
Dysesthesia	1(0·03) [1]	0	1(0·02) [1]
Head discomfort	1(0·03) [1]	0	1(0·02) [1]
Lethargy	1(0·03) [1]	0	1(0·02) [1]
Migraine	1(0·03) [1]	0	1(0·02) [1]
Migraine with aura	1(0·03) [1]	0	1(0·02) [1]
Neuralgia	1(0·03) [1]	0	1(0·02) [1]
General disorders and administration site conditions	58(1·91) [82]	19(1·91) [21]	77(1·91) [103]
Pain	13(0·43) [14]	1(0·10) [1]	14(0·35) [15]
Injection site pruritus	11(0·36) [14]	2(0·20) [2]	13(0·32) [16]
Chest pain	9(0·30) [10]	4(0·40) [5]	13(0·32) [15]
Chest discomfort	6(0·20) [7]	2(0·20) [2]	8(0·20) [9]
Pyrexia	4(0·13) [4]	3(0·30) [3]	7(0·17) [7]
Fatigue	4(0·13) [4]	1(0·10) [1]	5(0·12) [5]
Injection site warmth	4(0·13) [5]	0	4(0·10) [5]
Chills	4(0·13) [4]	0	4(0·10) [4]

System organ class Preferred term	GBP510 (N=3029)	ChAdOx1-S (N=996)	Total (N=4025)
Asthenia	2(0·07) [2]	1(0·10) [1]	3(0·07) [3]
Injection site bruising	3(0·10) [3]	0	3(0·07) [3]
Injection site pain	1(0·03) [1]	2(0·20) [2]	3(0·07) [3]
Feeling hot	2(0·07) [2]	0	2(0·05) [2]
Malaise	1(0·03) [1]	1(0·10) [1]	2(0·05) [2]
Injection site urticaria	1(0·03) [2]	0	1(0·02) [2]
Axillary pain	0	1(0·10) [1]	1(0·02) [1]
Facial discomfort	0	1(0·10) [1]	1(0·02) [1]
Feeling abnormal	1(0·03) [1]	0	1(0·02) [1]
Injection site erythema	1(0·03) [1]	0	1(0·02) [1]
Injection site hypoesthesia	0	1(0·10) [1]	1(0·02) [1]
Injection site muscle weakness	1(0·03) [1]	0	1(0·02) [1]
Injection site rash	1(0·03) [1]	0	1(0·02) [1]
Oedema peripheral	1(0·03) [1]	0	1(0·02) [1]
Swelling	1(0·03) [1]	0	1(0·02) [1]
Thirst	1(0·03) [1]	0	1(0·02) [1]
Vaccination site discomfort	1(0·03) [1]	0	1(0·02) [1]
Vaccination site pruritus	1(0·03) [1]	0	1(0·02) [1]
Musculoskeletal and connective tissue disorders	59(1·95) [76]	18(1·81) [21]	77(1·91) [97]
Arthralgia	12(0·40) [15]	3(0·30) [4]	15(0·37) [19]
Back pain	10(0·33) [10]	5(0·50) [5]	15(0·37) [15]
Myalgia	12(0·40) [14]	2(0·20) [2]	14(0·35) [16]
Pain in extremity	9(0·30) [11]	0	9(0·22) [11]
Groin pain	4(0·13) [4]	0	4(0·10) [4]
Muscle spasms	1(0·03) [1]	2(0·20) [2]	3(0·07) [3]
Musculoskeletal chest pain	2(0·07) [2]	1(0·10) [1]	3(0·07) [3]
Musculoskeletal stiffness	2(0·07) [3]	0	2(0·05) [3]
Flank pain	2(0·07) [2]	0	2(0·05) [2]
Limb discomfort	2(0·07) [2]	0	2(0·05) [2]
Rotator cuff syndrome	1(0·03) [1]	1(0·10) [1]	2(0·05) [2]
Temporomandibular joint syndrome	1(0·03) [1]	1(0·10) [1]	2(0·05) [2]
Fibromyalgia	0	1(0·10) [2]	1(0·02) [2]

System organ class Preferred term	GBP510 (N=3029)	ChAdOx1-S (N=996)	Total (N=4025)
Arthritis	1(0·03) [1]	0	1(0·02) [1]
Axillary mass	1(0·03) [1]	0	1(0·02) [1]
Costochondritis	1(0·03) [1]	0	1(0·02) [1]
Intervertebral disc protrusion	0	1(0·10) [1]	1(0·02) [1]
Muscle fatigue	1(0·03) [1]	0	1(0·02) [1]
Muscle oedema	1(0·03) [1]	0	1(0·02) [1]
Muscle twitching	1(0·03) [1]	0	1(0·02) [1]
Muscular weakness	1(0·03) [1]	0	1(0·02) [1]
Musculoskeletal pain	1(0·03) [1]	0	1(0·02) [1]
Myofascial pain syndrome	0	1(0·10) [1]	1(0·02) [1]
Neck pain	1(0·03) [1]	0	1(0·02) [1]
Soft tissue mass	0	1(0·10) [1]	1(0·02) [1]
Synovial cyst	1(0·03) [1]	0	1(0·02) [1]
Respiratory, thoracic and mediastinal disorders	43(1·42) [56]	19(1·91) [25]	62(1·54) [81]
Cough	17(0·56) [18]	6(0·60) [6]	23(0·57) [24]
Rhinorrhoea	12(0·40) [12]	7(0·70) [7]	19(0·47) [19]
Oropharyngeal pain	13(0·43) [14]	5(0·50) [5]	18(0·45) [19]
Dyspnoea	1(0·03) [1]	3(0·30) [3]	4(0·10) [4]
Rhinitis allergic	4(0·13) [4]	0	4(0·10) [4]
Allergic cough	2(0·07) [2]	1(0·10) [1]	3(0·07) [3]
Asthma	1(0·03) [1]	1(0·10) [2]	2(0·05) [3]
Productive cough	1(0·03) [1]	1(0·10) [1]	2(0·05) [2]
Dysphonia	1(0·03) [1]	0	1(0·02) [1]
Nasal congestion	1(0·03) [1]	0	1(0·02) [1]
Nasal dryness	1(0·03) [1]	0	1(0·02) [1]
Gastrointestinal disorders	37(1·22) [45]	17(1·71) [19]	54(1·34) [64]
Toothache	8(0·26) [9]	1(0·10) [1]	9(0·22) [10]
Gastroesophageal reflux disease	4(0·13) [4]	3(0·30) [3]	7(0·17) [7]
Abdominal pain upper	1(0·03) [1]	5(0·50) [5]	6(0·15) [6]
Dyspepsia	4(0·13) [4]	2(0·20) [2]	6(0·15) [6]
Diarrhoea	5(0·17) [6]	0	5(0·12) [6]
Stomatitis	2(0·07) [3]	2(0·20) [2]	4(0·10) [5]

System organ class Preferred term	GBP510 (N=3029)	ChAdOx1-S (N=996)	Total (N=4025)
Abdominal pain	3(0·10) [3]	1(0·10) [1]	4(0·10) [4]
Mouth ulceration	2(0·07) [2]	1(0·10) [1]	3(0·07) [3]
Nausea	2(0·07) [3]	0	2(0·05) [3]
Gastritis	1(0·03) [1]	1(0·10) [1]	2(0·05) [2]
Anal haemorrhage	1(0·03) [1]	0	1(0·02) [1]
Aphthous ulcer	0	1(0·10) [1]	1(0·02) [1]
Cheilitis	1(0·03) [1]	0	1(0·02) [1]
Colitis	1(0·03) [1]	0	1(0·02) [1]
Gingival bleeding	1(0·03) [1]	0	1(0·02) [1]
Gingival swelling	1(0·03) [1]	0	1(0·02) [1]
Glossitis	1(0·03) [1]	0	1(0·02) [1]
Haematochezia	1(0·03) [1]	0	1(0·02) [1]
Haemorrhoids	1(0·03) [1]	0	1(0·02) [1]
Lip blister	0	1(0·10) [1]	1(0·02) [1]
Pancreatitis acute	0	1(0·10) [1]	1(0·02) [1]
Vomiting	1(0·03) [1]	0	1(0·02) [1]
Skin and subcutaneous tissue disorders	23(0·76) [25]	6(0·60) [7]	29(0·72) [32]
Rash	7(0·23) [7]	0	7(0·17) [7]
Urticaria	5(0·17) [6]	1(0·10) [1]	6(0·15) [7]
Pruritus	5(0·17) [5]	1(0·10) [1]	6(0·15) [6]
Hyperhidrosis	2(0·07) [2]	2(0·20) [2]	4(0·10) [4]
Cold sweat	1(0·03) [1]	2(0·20) [2]	3(0·07) [3]
Alopecia	0	1(0·10) [1]	1(0·02) [1]
Blister	1(0·03) [1]	0	1(0·02) [1]
Dermatitis	1(0·03) [1]	0	1(0·02) [1]
Dermatitis atopic	1(0·03) [1]	0	1(0·02) [1]
Night sweats	1(0·03) [1]	0	1(0·02) [1]
Injury, poisoning and procedural complications	18(0·59) [20]	6(0·60) [6]	24(0·60) [26]
Skin laceration	5(0·17) [5]	0	5(0·12) [5]
Arthropod sting	3(0·10) [3]	0	3(0·07) [3]
Joint injury	2(0·07) [2]	1(0·10) [1]	3(0·07) [3]
Hand fracture	2(0·07) [2]	0	2(0·05) [2]

System organ class Preferred term	GBP510 (N=3029)	ChAdOx1-S (N=996)	Total (N=4025)
Limb injury	0	2(0·20) [2]	2(0·05) [2]
Skin abrasion	1(0·03) [1]	1(0·10) [1]	2(0·05) [2]
Contusion	1(0·03) [2]	0	1(0·02) [2]
Concussion	1(0·03) [1]	0	1(0·02) [1]
Epicondylitis	1(0·03) [1]	0	1(0·02) [1]
Joint dislocation	0	1(0·10) [1]	1(0·02) [1]
Ligament sprain	0	1(0·10) [1]	1(0·02) [1]
Muscle strain	1(0·03) [1]	0	1(0·02) [1]
Post-traumatic pain	1(0·03) [1]	0	1(0·02) [1]
Wound	1(0·03) [1]	0	1(0·02) [1]
Reproductive system and breast disorders	11(0·36) [15]	6(0·60) [6]	17(0·42) [21]
Dysmenorrhoea	5(0·17) [6]	2(0·20) [2]	7(0·17) [8]
Vaginal haemorrhage	1(0·03) [1]	2(0·20) [2]	3(0·07) [3]
Premenstrual syndrome	2(0·07) [2]	0	2(0·05) [2]
Cervix inflammation	1(0·03) [1]	0	1(0·02) [1]
Genital pain	1(0·03) [1]	0	1(0·02) [1]
Menstrual disorder	1(0·03) [1]	0	1(0·02) [1]
Menstruation irregular	1(0·03) [1]	0	1(0·02) [1]
Polymenorrhea	1(0·03) [1]	0	1(0·02) [1]
Testicular pain	1(0·03) [1]	0	1(0·02) [1]
Vaginal discharge	0	1(0·10) [1]	1(0·02) [1]
Vulvovaginal inflammation	0	1(0·10) [1]	1(0·02) [1]
Ear and labyrinth disorders	10(0·33) [10]	2(0·20) [2]	12(0·30) [12]
Ear discomfort	2(0·07) [2]	1(0·10) [1]	3(0·07) [3]
Ear pain	3(0·10) [3]	0	3(0·07) [3]
Vertigo	2(0·07) [2]	0	2(0·05) [2]
Cerumen impaction	1(0·03) [1]	0	1(0·02) [1]
Ear disorder	1(0·03) [1]	0	1(0·02) [1]
Motion sickness	1(0·03) [1]	0	1(0·02) [1]
Tinnitus	0	1(0·10) [1]	1(0·02) [1]
Vascular disorders	8(0·26) [8]	3(0·30) [3]	11(0·27) [11]
Hypertension	6(0·20) [6]	3(0·30) [3]	9(0·22) [9]

System organ class Preferred term	GBP510 (N=3029)	ChAdOx1-S (N=996)	Total (N=4025)
Flushing	1(0·03) [1]	0	1(0·02) [1]
Lymphoedema	1(0·03) [1]	0	1(0·02) [1]
Cardiac disorders	6(0·20) [7]	4(0·40) [4]	10(0·25) [11]
Palpitations	5(0·17) [5]	3(0·30) [3]	8(0·20) [8]
Acute myocardial infarction	1(0·03) [1]	0	1(0·02) [1]
Atrioventricular block second degree	1(0·03) [1]	0	1(0·02) [1]
Cardiopulmonary failure	0	1(0·10) [1]	1(0·02) [1]
Eye disorders	6(0·20) [7]	3(0·30) [3]	9(0·22) [10]
Vision blurred	0	2(0·20) [2]	2(0·05) [2]
Eye allergy	1(0·03) [2]	0	1(0·02) [2]
Dry eye	1(0·03) [1]	0	1(0·02) [1]
Eye haemorrhage	1(0·03) [1]	0	1(0·02) [1]
Eye pain	0	1(0·10) [1]	1(0·02) [1]
Eye pruritus	1(0·03) [1]	0	1(0·02) [1]
Eye swelling	1(0·03) [1]	0	1(0·02) [1]
Keratitis	1(0·03) [1]	0	1(0·02) [1]
Metabolism and nutrition disorders	8(0·26) [10]	0	8(0·20) [10]
Decreased appetite	5(0·17) [6]	0	5(0·12) [6]
Obesity	2(0·07) [2]	0	2(0·05) [2]
Diabetes mellitus	1(0·03) [1]	0	1(0·02) [1]
Dyslipidaemia	1(0·03) [1]	0	1(0·02) [1]
Immune system disorders	4(0·13) [5]	1(0·10) [1]	5(0·12) [6]
Hypersensitivity	1(0·03) [1]	1(0·10) [1]	2(0·05) [2]
Food allergy	1(0·03) [2]	0	1(0·02) [2]
Allergy to arthropod bite	1(0·03) [1]	0	1(0·02) [1]
Allergy to plants	1(0·03) [1]	0	1(0·02) [1]
Renal and urinary disorders	3(0·10) [4]	2(0·20) [2]	5(0·12) [6]
Ureterolithiasis	1(0·03) [1]	1(0·10) [1]	2(0·05) [2]
Acute kidney injury	1(0·03) [1]	0	1(0·02) [1]
Chronic kidney disease	1(0·03) [1]	0	1(0·02) [1]
Glomerulonephritis rapidly progressive	1(0·03) [1]	0	1(0·02) [1]
Proteinuria	0	1(0·10) [1]	1(0·02) [1]

System organ class Preferred term	GBP510 (N=3029)	ChAdOx1-S (N=996)	Total (N=4025)
Blood and lymphatic system disorders	4(0·13) [4]	0	4(0·10) [4]
Lymphadenopathy	2(0·07) [2]	0	2(0·05) [2]
Anaemia	1(0·03) [1]	0	1(0·02) [1]
Lymph node pain	1(0·03) [1]	0	1(0·02) [1]
Psychiatric disorders	4(0·13) [4]	0	4(0·10) [4]
Euphoric mood	1(0·03) [1]	0	1(0·02) [1]
Insomnia	1(0·03) [1]	0	1(0·02) [1]
Schizophrenia	1(0·03) [1]	0	1(0·02) [1]
Sleep disorder	1(0·03) [1]	0	1(0·02) [1]
Surgical and medical procedures	3(0·10) [3]	1(0·10) [1]	4(0·10) [4]
Tooth extraction	2(0·07) [2]	0	2(0·05) [2]
Dental implantation	0	1(0·10) [1]	1(0·02) [1]
Wisdom teeth removal	1(0·03) [1]	0	1(0·02) [1]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1(0·03) [1]	1(0·10) [1]	2(0·05) [2]
Melanocytic naevus	1(0·03) [1]	0	1(0·02) [1]
Uterine leiomyoma	0	1(0·10) [1]	1(0·02) [1]
Hepatobiliary disorders	0	1(0·10) [2]	1(0·02) [2]
Cholangitis acute	0	1(0·10) [1]	1(0·02) [1]
Cholecystitis acute	0	1(0·10) [1]	1(0·02) [1]
Investigations	1(0·03) [1]	0	1(0·02) [1]
Serum ferritin decreased	1(0·03) [1]	0	1(0·02) [1]

AEs = adverse events.

MedDRA version: 24.0.

Data are presented as 'number of participants (% participants) [number of events]'. Denominator of percentage is the number of participants in each group. 95% confidence interval was calculated by Clopper-Pearson Methods.

[1] Testing for between-treatment groups (chi-square test (c) or Fisher's exact test (f)).

COVID-19 confirmed cases were diagnosed by the virological (PCR) test. COVID-19 cases diagnosed by the rapid antibody, and not confirmed via PCR, are considered suspected COVID-19 cases.

Table S38. Unsolicited AEs with ≥ Grade 3 Severity by System Organ Class / Preferred Term Safety Set [Up to 4 weeks after 2nd vaccination]

System organ class Preferred term	GBP510 (N=3029)	ChAdOx1-S (N=996)	Total (N=4025)
Participants with Unsolicited AEs with ≥ Grade 3 Severity	20(0·66) [27]	12(1·20) [18]	32(0·80) [45]
Exact 95% Confidence Interval	[0·40, 1·02]	[0·62, 2·10]	[0·54, 1·12]
P-value [1]			0·09 (c)
Gastrointestinal disorders	3(0·10) [3]	5(0·50) [5]	8(0·20) [8]
Gastroesophageal reflux disease	1(0·03) [1]	1(0·10) [1]	2(0·05) [2]
Abdominal pain	0	1(0·10) [1]	1(0·02) [1]
Abdominal pain upper	0	1(0·10) [1]	1(0·02) [1]
Colitis	1(0·03) [1]	0	1(0·02) [1]
Dyspepsia	0	1(0·10) [1]	1(0·02) [1]
Haemorrhoids	1(0·03) [1]	0	1(0·02) [1]
Stomatitis	0	1(0·10) [1]	1(0·02) [1]
Infections and infestations	5(0·17) [6]	1(0·10) [2]	6(0·15) [8]
Rhinitis	1(0·03) [1]	1(0·10) [1]	2(0·05) [2]
Gastroenteritis	1(0·03) [1]	0	1(0·02) [1]
Laryngopharyngitis	1(0·03) [1]	0	1(0·02) [1]
Nasopharyngitis	0	1(0·10) [1]	1(0·02) [1]
Pneumonia	1(0·03) [1]	0	1(0·02) [1]
Upper respiratory tract infection	1(0·03) [1]	0	1(0·02) [1]
Urinary tract infection	1(0·03) [1]	0	1(0·02) [1]
General disorders and administration site conditions	3(0·10) [3]	2(0·20) [2]	5(0·12) [5]
Pain	2(0·07) [2]	0	2(0·05) [2]
Asthenia	0	1(0·10) [1]	1(0·02) [1]
Chest pain	0	1(0·10) [1]	1(0·02) [1]
Chills	1(0·03) [1]	0	1(0·02) [1]
Musculoskeletal and connective tissue disorders	3(0·10) [3]	2(0·20) [2]	5(0·12) [5]
Arthralgia	0	1(0·10) [1]	1(0·02) [1]
Back pain	1(0·03) [1]	0	1(0·02) [1]
Myalgia	1(0·03) [1]	0	1(0·02) [1]
Pain in extremity	1(0·03) [1]	0	1(0·02) [1]

System organ class Preferred term	GBP510 (N=3029)	ChAdOx1-S (N=996)	Total (N=4025)
Rotator cuff syndrome	0	1(0·10) [1]	1(0·02) [1]
Nervous system disorders	2(0·07) [2]	1(0·10) [1]	3(0·07) [3]
Paraesthesia	1(0·03) [1]	1(0·10) [1]	2(0·05) [2]
Headache	1(0·03) [1]	0	1(0·02) [1]
Respiratory, thoracic and mediastinal disorders	2(0·07) [2]	1(0·10) [1]	3(0·07) [3]
Asthma	1(0·03) [1]	0	1(0·02) [1]
Dyspnoea	0	1(0·10) [1]	1(0·02) [1]
Oropharyngeal pain	1(0·03) [1]	0	1(0·02) [1]
Skin and subcutaneous tissue disorders	3(0·10) [3]	0	3(0·07) [3]
Dermatitis atopic	1(0·03) [1]	0	1(0·02) [1]
Rash	1(0·03) [1]	0	1(0·02) [1]
Urticaria	1(0·03) [1]	0	1(0·02) [1]
Cardiac disorders	1(0·03) [1]	1(0·10) [1]	2(0·05) [2]
Acute myocardial infarction	1(0·03) [1]	0	1(0·02) [1]
Cardiopulmonary failure	0	1(0·10) [1]	1(0·02) [1]
Renal and urinary disorders	1(0·03) [1]	1(0·10) [1]	2(0·05) [2]
Glomerulonephritis rapidly progressive	1(0·03) [1]	0	1(0·02) [1]
Ureterolithiasis	0	1(0·10) [1]	1(0·02) [1]
Surgical and medical procedures	1(0·03) [1]	1(0·10) [1]	2(0·05) [2]
Dental implantation	0	1(0·10) [1]	1(0·02) [1]
Tooth extraction	1(0·03) [1]	0	1(0·02) [1]
Hepatobiliary disorders	0	1(0·10) [2]	1(0·02) [2]
Cholangitis acute	0	1(0·10) [1]	1(0·02) [1]
Cholecystitis acute	0	1(0·10) [1]	1(0·02) [1]
Injury, poisoning and procedural complications	1(0·03) [1]	0	1(0·02) [1]
Skin laceration	1(0·03) [1]	0	1(0·02) [1]
Reproductive system and breast disorders	1(0·03) [1]	0	1(0·02) [1]
Premenstrual syndrome	1(0·03) [1]	0	1(0·02) [1]

AEs = adverse events.

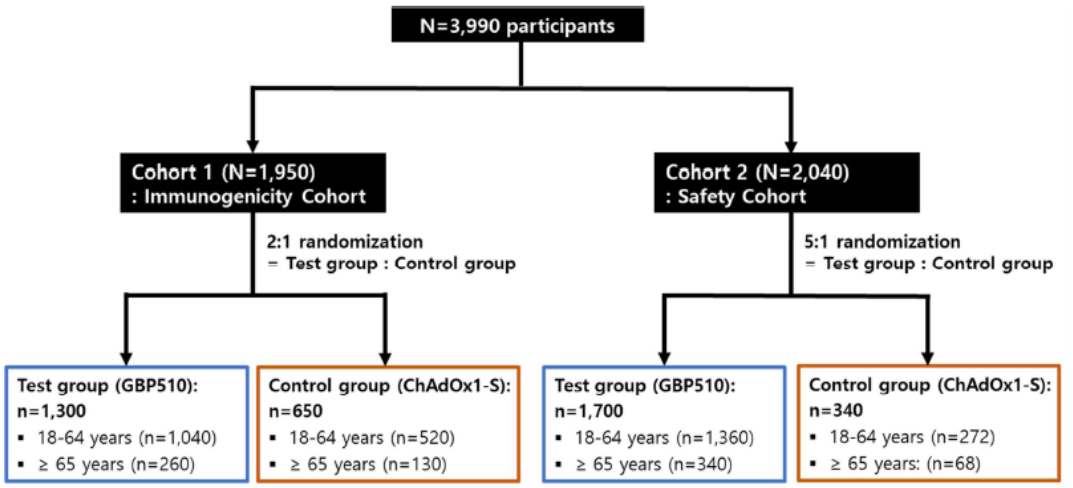
MedDRA version: 24.0.

Data are presented as 'number of participants (% participants) [number of events]'. Denominator of percentage is the number of participants in each group. 95% confidence interval was calculated by Clopper-Pearson Methods.

[1] Testing for between-treatment groups (chi-square test (c) or Fisher's exact test (f))..

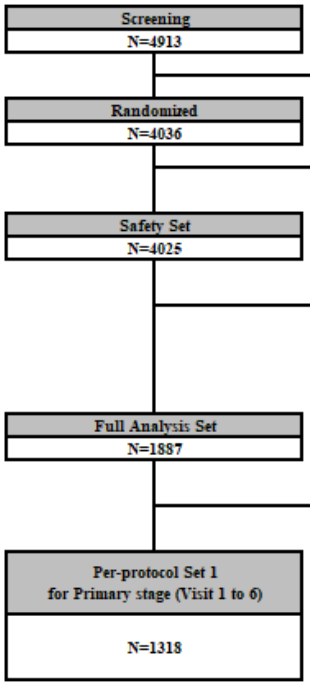
II. Supplementary Figures

Figure S1. Schema of Study Enrolment



* Approximately 20% of the participants in each treatment group was planned to be elderly population aged 65 years or older

Figure S2. Analysis Sets (Up to 4 weeks after 2nd vaccination)



Screening Failure	
N=877	

Excluded from Safety Set			
N=11			
GBP510		ChAdOx1-S	
N=9		N=2	
Not treated	N=9	Not treated	N=2

Excluded from Full Analysis Set			
N=2138			
GBP510		ChAdOx1-S	
N=1771		N=367	
No valid both pre- and at least one post-vaccination immunogenicity assessment results	N=40	No valid both pre- and at least one post-vaccination immunogenicity assessment results	N=21
Cohort 2	N=1731	Cohort 2	N=346

Excluded from Per-protocol Set 1 for Primary stage (Visit 1 to 6)			
N=569			
GBP510		ChAdOx1-S	
N=382		N=187	
Participant did not meet all inclusion criteria or met at least one of the exclusion criteria	1	Participant did not meet all inclusion criteria or met at least one of the exclusion criteria	1
Participant did not complete the vaccination schedule	3	Preparation and / or administration of study intervention was not done as per-protocol	9
Preparation and / or administration of study intervention was not done as per-protocol	13	Any of the blood samples were not drawn, or not drawn in the proper time window until Visit 6 (Day 14+3 after Visit 4)	47
Any of the blood samples were not drawn, or not drawn in the proper time window until Visit 6 (Day 14+3 after Visit 4)	94	Participant with FRNT value at baseline is above LLOQ	54
Participant received a protocol-prohibited medication or vaccine from Visit 2 (Day 0) to Visit 6 (Day 14+3 after Visit 4) (see Section 6.7.1)	1	With positive for SARS-CoV-2 Ab N-protein test	66
Participant with FRNT value at baseline is above LLOQ	113	Participant with confirmed/suspected COVID-19	8
With positive for SARS-CoV-2 Ab N-protein test	141	Withdrawal before Visit 6	2
No result for Immunoassay for SARS-CoV-2 at V6	1		
Participant with confirmed/suspected COVID-19	12		
Withdrawal before Visit 6	3		

Figure S3. Boxplot for the Natural Logarithmic of Titre by ELISA at Visit 2, 4, and 6 (Per-Protocol Set)

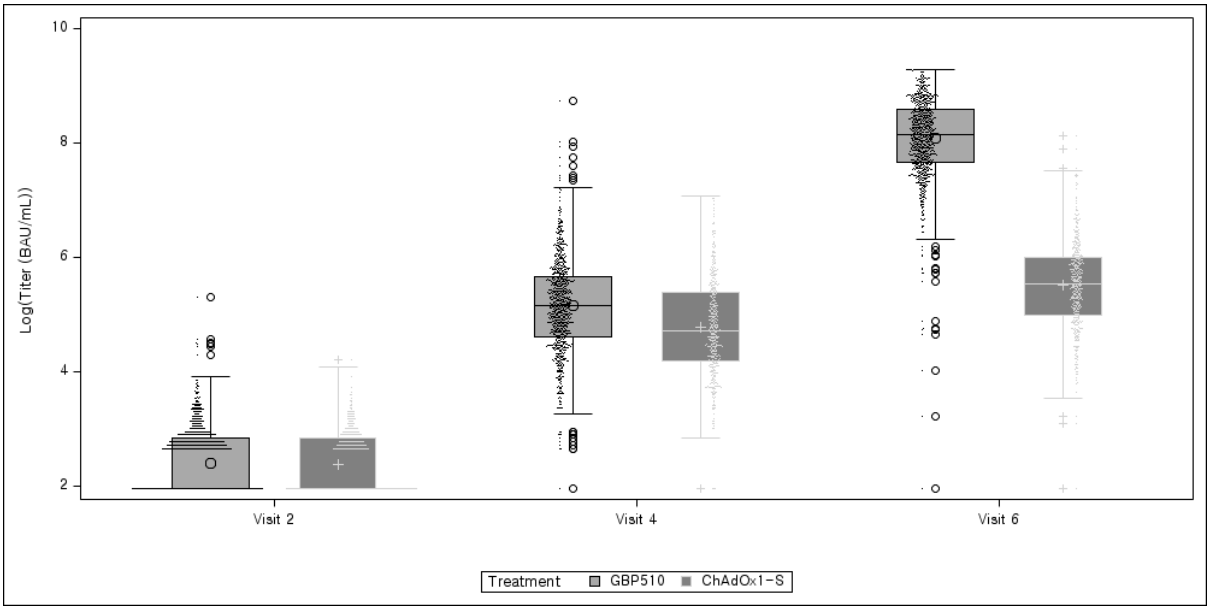


Figure S4. Cell-mediated Response FluoroSpot Assay (Per-Protocol Set) [T cell: IFNγ]

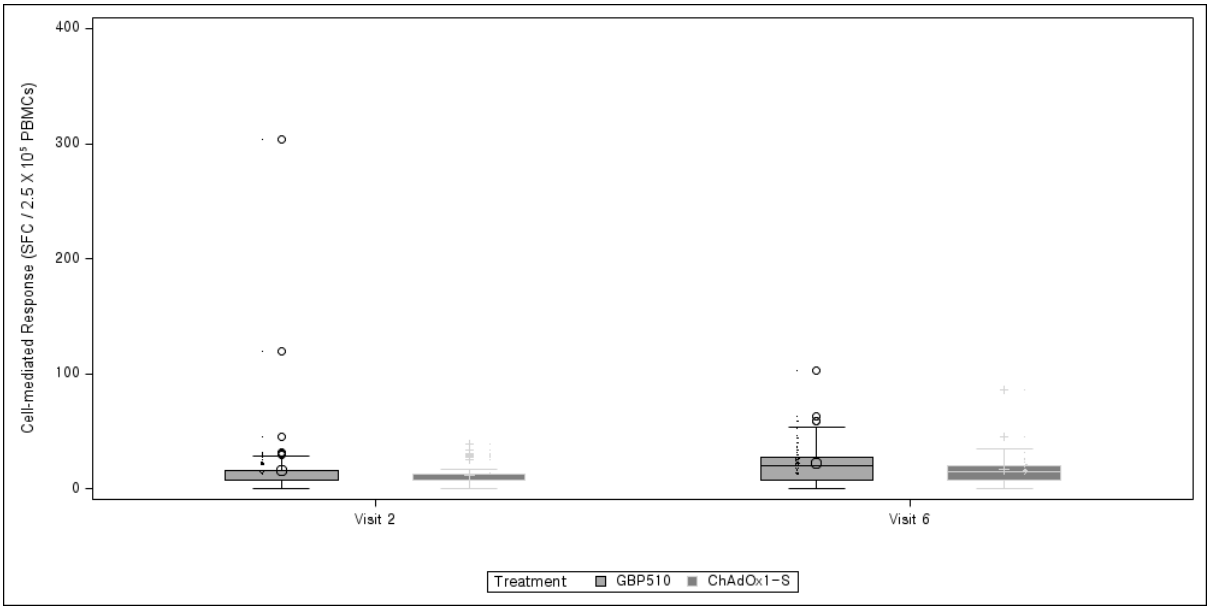


Figure S5. Cell-mediated Response FluoroSpot Assay (Per-Protocol Set) [T cell: IL-2]

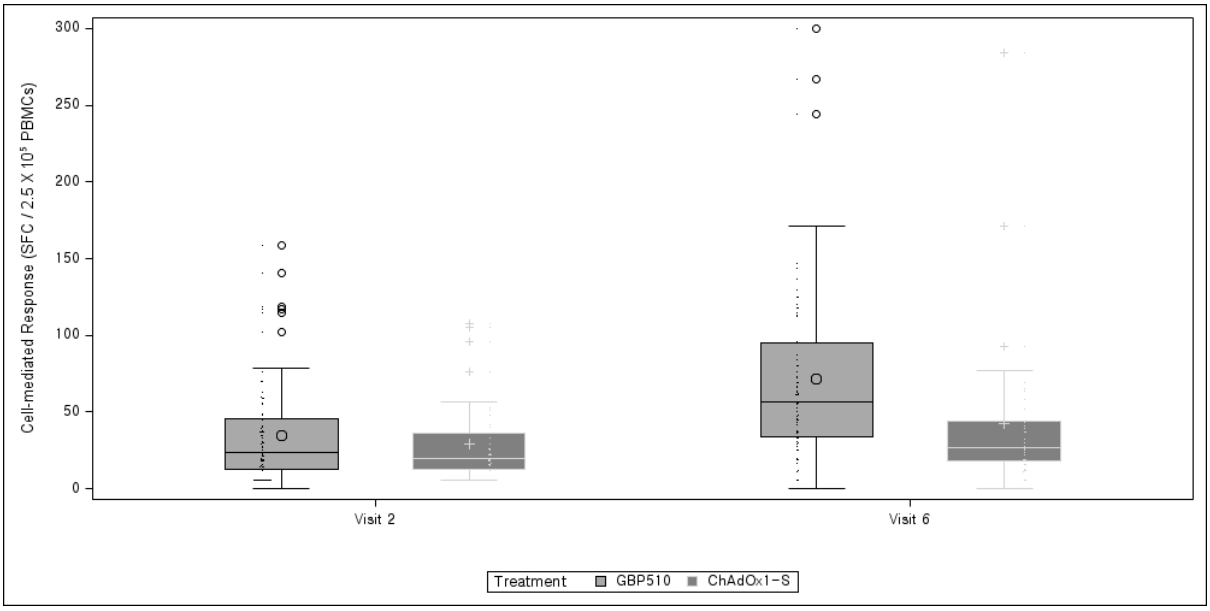


Figure S6. Cell-mediated Response FluoroSpot Assay (Per-Protocol Set) [T cell: TNFα]

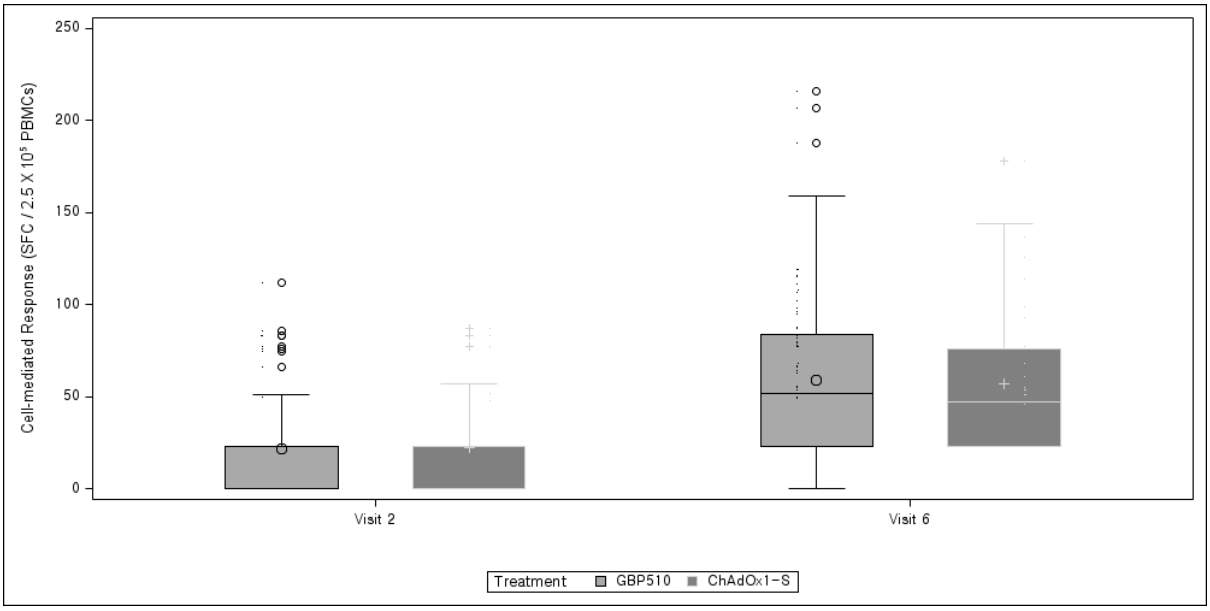


Figure S7. Cell-mediated Response FluoroSpot Assay (Per-Protocol Set) [T cell: IL-4]

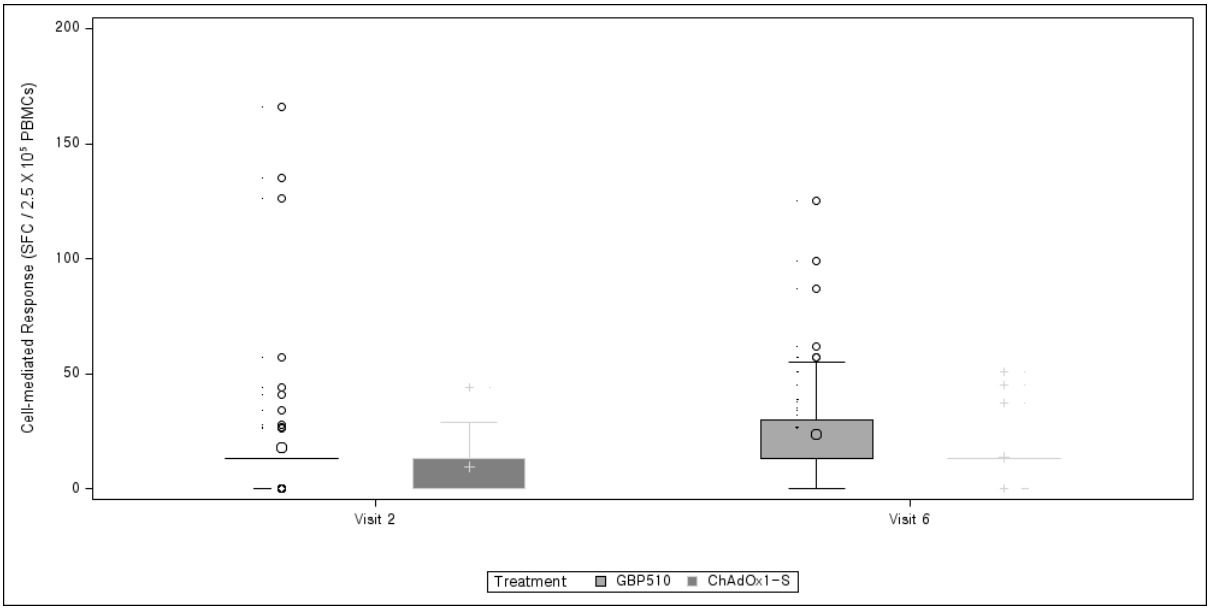


Figure S8. Cell-mediated Response FACS (Per-Protocol Set) [CD4+ T cell: IFNγ]

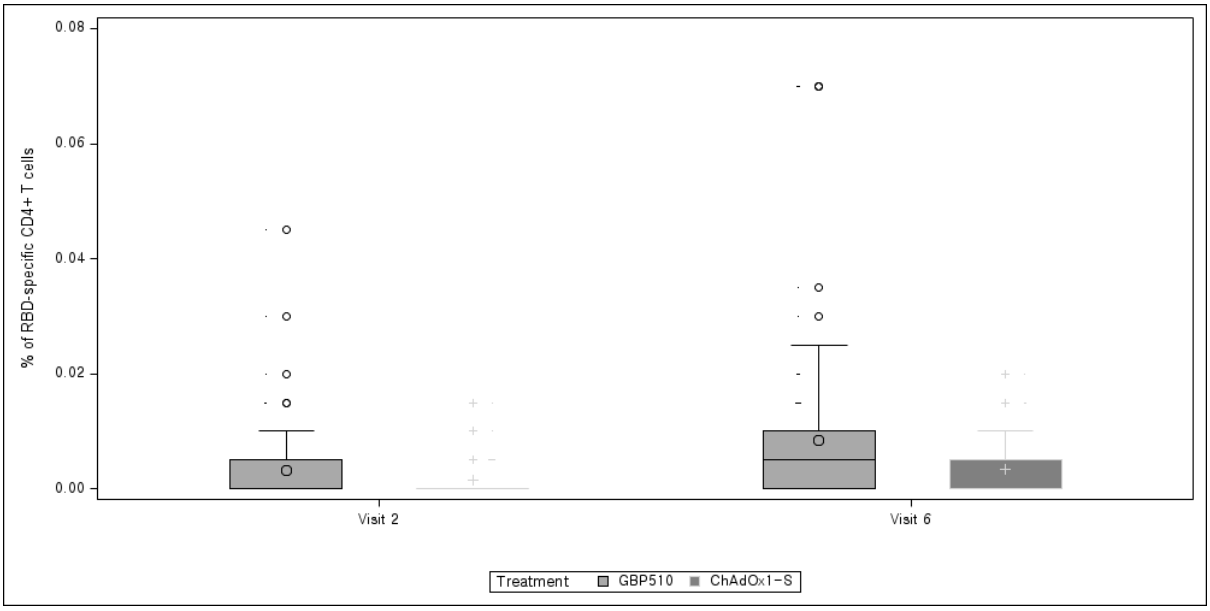


Figure S9. Cell-mediated Response FACS (Per-Protocol Set) [CD4+ T cell: IL-2]

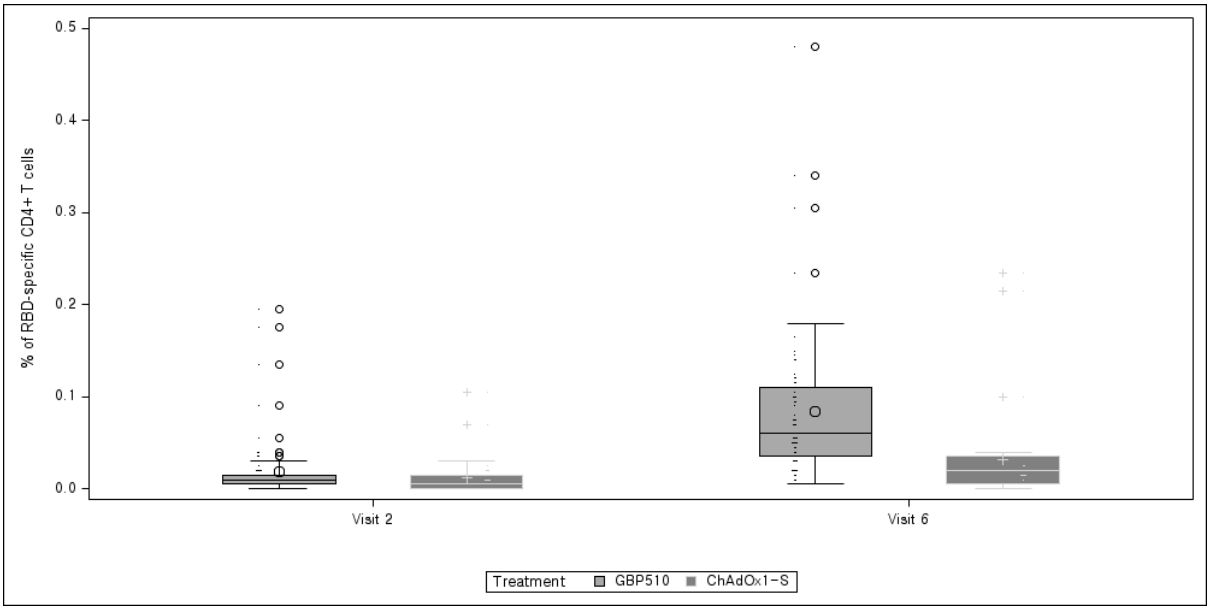


Figure S10. Cell-mediated Response FACS (Per-Protocol Set) [CD4+ T cell: TNFα]

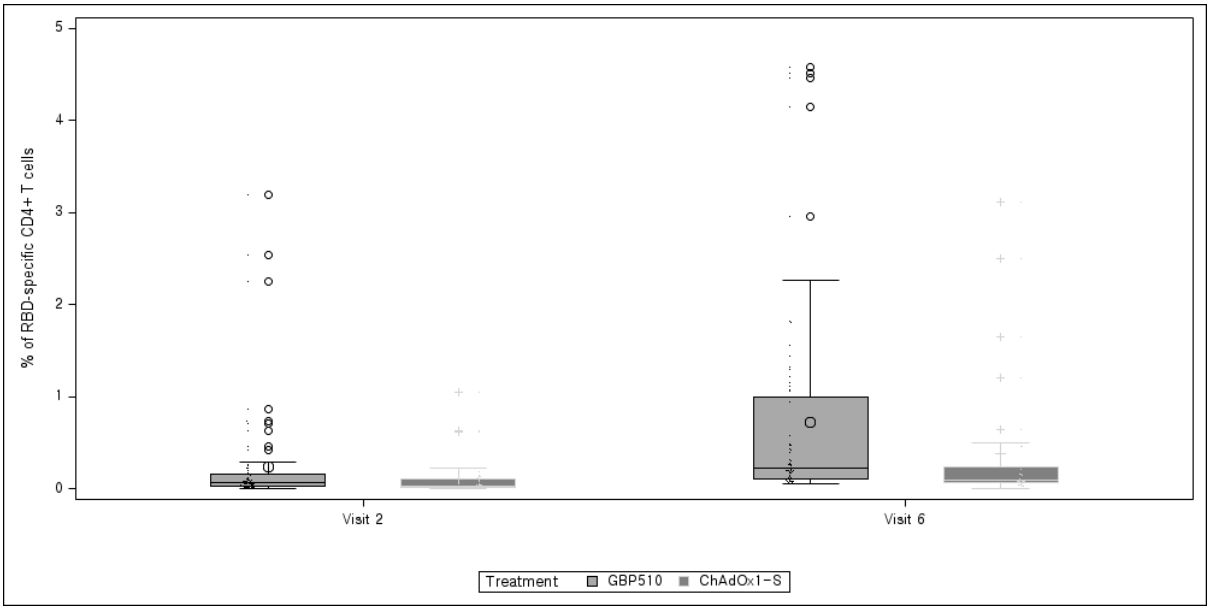
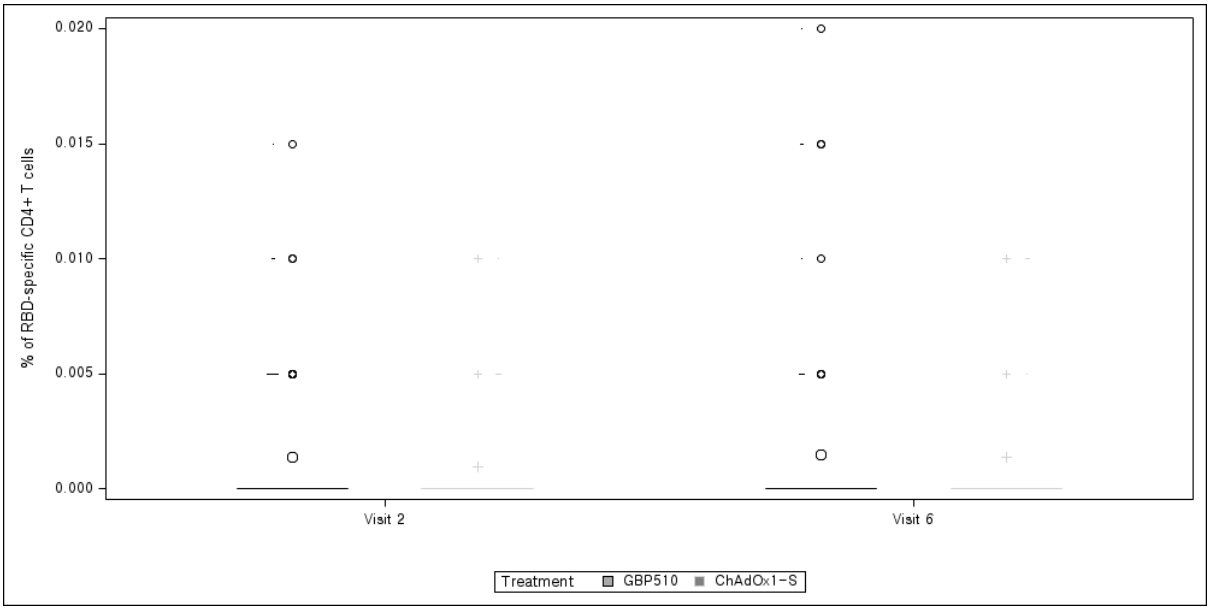


Figure S11. Cell-mediated Response FACS (Per-Protocol Set) [CD4+ T cell: IL-4]



III. Narratives of Death Cases

One of the participants who reported 'death' experienced a SAE of 'Cardiopulmonary failure' (MedDRA LLT: Cardiopulmonary failure) and passed away. At screening visit, the participant's blood pressure was abnormally high at 200/100mmHg. The participant received his first test vaccine administration and at that time, the blood pressure was still abnormally high at 190/100mmHg. It was assessed as non-clinically significant by the investigator, since the participant health status was in normal ranges for all other systems and was in good health condition. The participant was also advised to consult with a cardio-specialist for the high blood pressure. The participant did not have any other abnormal symptoms or adverse events after the first vaccine administration, approximately for a week. Approximately after a month of first vaccination, it was reported that the participant had passed away, due to cardio-respiratory failure, verified by the death certificate. No autopsy was performed. It was confirmed that the participant never received any medical treatment from another hospital or health care unit. Based on the limited information provided, there was no sufficient evidence to support a causal relationship between the events 'Cardiopulmonary failure' and the vaccine administered. According to the documented blood pressure results at the screening visit and first test vaccine administration, the participant had an uncontrollable hypertension. Thus, by considering the patient's concurrent condition, this SAE was assessed as 'not related' to the vaccine by the investigator and sponsor.

One of the participants who reported 'death' experienced a SAE of 'Brain neoplasm' (MedDRA LLT: Brain tumor). The participant was administrated with 2 doses of test vaccine at a 4-week interval. Approximately after 80 days, the participant started to experiencing headache and fatigue. Due to these symptoms, the participant visited the hospital for medical examination and was prescribed with unknown type of treatment medications. At that time, the participant was not admitted to the hospital and was monitored at home. Four days later, the participant admitted to the hospital due to worsening of the symptoms which accompanied weakness on the left side of the body. The participant was diagnosed with a severe brain tumor via the result of CT scan. After 3 days of hospitalization, the participant was discharged from the hospital due to financial issues, although the severity of event was not reduced. A day after, the participant passed away. The participant had no medical or surgical history relevant with brain tumor. Considering the pathology of brain tumors that it takes quite a long time to develop and to be diagnosed, the participant and the investigator may have not recognized the participant's brain tumor at the study enrollment. Therefore, this SAE was assessed as 'not related' to the vaccine by the investigator and sponsor.

One of the participants who reported 'death' experienced SAEs of 'Tubulointerstitial nephritis' and 'Acute cholecystitis'. The participant was administrated with 2 doses of test vaccine at a 4-week interval. The subject's concomitant medication included Enalapril 20 mg (ongoing indication: hypertension) and Simvastatin 40 mg (ongoing indication: hyperlipidemia). It was reported that the participant is dead approximately 5 months after the second vaccination. It was reported that the participant had fatigue, loss of appetite, and icteric sclera for about a week and severe abdominal pain, started approximately 45 days before passed away. No autopsy was conducted, and it was not able to obtain lab report due to the internal policy of the private hospital the participant was hospitalized in. However, it is well known that [LLT: Acute cholecystitis] occurs when bile becomes trapped in the gallbladder, and it often occurs because a gallstone blocks the cystic duct. Furthermore, the participant had a medical history of hyperlipidemia since 2016, which is well known fact that high blood serum lipid levels contribute to the pathogenesis of gallbladder stones. Therefore, even though limited information collected, this 'death' case was assessed as 'not related' to the test vaccine by the investigator and sponsor, considering the medical history of participant and the long gap between the 'death' case and second IP administration date.

IV. Narratives of Study Withdrawal Due to AEs

There was a total of 5 participants (3 participants in GBP510 group and 2 participants in ChAdOx1-S group) withdrawn due to AEs up to Visit 7 (Day 28+5 after 2nd study vaccination). Total 6 events (occurred in one participant) were reported as 'related to study vaccine'. No additional cases were reported after Visit 7 to 6 months of follow-up after 2nd vaccination.

One participant from ChAdOx1-S group received the 1st vaccination and reported 'Upper respiratory tract infection'(Grade 1) and 'Pneumonia'. 'Upper respiratory tract infection' started approximately 30 days after the first vaccination, which lasted for four days and reported as 'Recovered/resolved'. 'Pneumonia' started approximately 35 days after first vaccination and reported as 'Not recovered/not resolved' (stabilized). Both cases were judged as 'not related to study vaccine'.

One participant from GBP510 group received the 1st vaccination and reported 'acute gastroenteritis' (Grade 1) approximately 25 days after, which lasted for two days. It was judged as 'not related to study vaccine' and recovered/resolved.

One participant from ChAdOx1-S group received the first vaccination and. The participant reported 2 SAEs (Acute Cholangitis and Acute Cholecystitis), which was judged as 'not related to study vaccine' and recovered/resolved. approximately 27 days after his first IP administration, the participant was admitted to the hospital due to the abdominal pain (The pain score was 8/10). Upon screening, the participant was diagnosed with acute cholecystitis and acute cholangitis. Through cholangiogram, pus and small stones were found. And by culture and sensitivity (C/S) of the bile specimen, streptococcus mitis was found. The participant gradually recovered from the pain and illness. Considering the pathological occurrence of both events ('Cholecystitis acute' and 'Cholangitis acute'), the SAEs were assessed as 'not related' to the IP (ChAdOx1-S) by the investigator and sponsor.

One participant from GBP510 group received the 1st vaccination and reported 'urticaria rash '(Grade 1), 'injection site pain' (Grade 3), 'headache' (Grade 1), 'fatigue' (Grade 2), 'myalgia' (Grade 2), and 'arthralgia' (Grade 1), which lasted from first day of vaccination, which lasted for 5 days. These were all judged as 'related to study vaccine' and recovered/resolved.

One participant from GBP510 group was withdrawn due to SAE of 'Schizophrenia' (MedDRA LLT: Paranoid schizophrenia). The participant was administrated with 0.5 mL of the first IP. Two days after first administration, the participant started showing behavioural changes such as having difficulty in sleep and occasional confusion. The participant had no previous medical history nor drug history relevant to the SAE. This event was reported as ongoing and has not been resolved. This event was assessed as 'not related' to the IP (GBP510) by the investigator and sponsor, since schizophrenia can be described as a neurodevelopmental disorder and it was confirmed in non-clinical studies that the IP did not affect the central nervous system.

V. Lists of Clinical Sites by Each Country

Country	Institution
Korea	Korea University Guro Hospital
	Korea University Ansan Hospital
	Ajou University Hospital
	Inha University Hospital
	Dong-A University Hospital
	Kyungpook National University Hospital
	Chonnam National University Hospital
	Gachen University Gil Medical Center
	Severance Hospital
	Hallym University Medical Center
	Kyungpook National University Chilgok Hospital
	Ewha Womans University Mokdong Hospital
	Korea University Anam Hospital
	Wonju Severance Christian Hospital
	Soonchunhyang University Seoul Hospital
	Seoul National University Hospital
Philippines	University of The East-Ramon Magsaysay Memorial Medical Center Inc.
	San Francisco Multi-Purpose Building
	Health Index Multispeciality Clinic
Thailand	Armed Forces Research Institute of Medical Sciences (AFRIMS)
	Faculty of Medicine Siriraj Hospital, Mahidol University: Siriraj Hospital
	Faculty of Medicine, Khon Kaen University: Sriganarind Hospital
	Faculty of Medicine, Chiang Mai University: Maharaj Nakorn Chiang Mai Hospital
Vietnam	Pasteur Institute in Hochiminh City
Ukraine	Medical Center “Ok!Clinic+” of the“International Institute for Clinical Studies”, LLC, outpatient department,
	Private Enterprise Private Manufacturing Company “Acinus”, Diagnostic and Treatment Center

	Communal non-profit enterprise "Kyiv city Hospital №6" of Executive Body of the Kyiv City Administration (Kyiv City State Administration)
	Municipal Nonprofit Enterprise "Khmelnytsky Regional Hospital for War Veterans" of Khmelnytsky Regional Council
	"Treatment and Diagnistic Center "Adonis-plus" LLC
	Medical Center of Preventclinic LLC
	LLC MC Blagomed
New Zealand	Southern Clinical Trials Tasman
	Southern Clinical Trials Christchurch
	Southern Clinical Trials Waitemata
	Lakeland Clinical Trials ROTORUA
	Lakeland Clinical Trials WAIKATO
	Lakeland Clinical Trials Wellington
	Lakeland Clinical Trials Culloden

VI. Study Protocol

Title Page

Protocol Title:
A Phase III, Randomized, Active-controlled, Observer-blind, Parallel-group, Multi-center Study to Assess the Immunogenicity and Safety of SK SARS-CoV-2 Recombinant Protein Nanoparticle Vaccine adjuvanted with AS03 (GBP510) in Adults Aged 18 Years and Older

Protocol Number: GBP510_003

Amendment Number: Not Applicable

Compound: GBP510

Brief Title: A Phase III Study to Assess the Immunogenicity and Safety of SK SARS-CoV-2 Recombinant Protein Nanoparticle Vaccine adjuvanted with AS03 (GBP510) in Adults Aged 18 Years and Older

Study Phase: Phase III

Study Participants: Healthy or medically stable adults aged 18 years and older

Legal Registered Address: 310 Pangyo-ro, Bundang-gu, Seongnam-si, Gyeonggi-do, 13494, South Korea

Manufacturer / Sponsor: SK bioscience Co., Ltd.

Co-sponsor: International Vaccine Institute (IVI)

IP Production Facility Address: 150 Andong L HOUSE Vaccine center, Saneopdanji-gil, Pungsan-eup, Andong-si, Gyeongsangbuk-do, 36618, South Korea

Regulatory Agency Identifier Number(s)

[redacted]

Approval Date: To be determined

Confidentiality Statement: The information presented in this protocol is exclusive property of SK bioscience Co., Ltd. and shall be treated as confidential. The access to such confidential information must be restricted to the recipient for agreed purpose and must not be disclosed to any party not involved in this clinical trial without prior written agreement or approval of SK bioscience. Co., Ltd.

Protocol Amendment Summary of Changes Table

Version Date	Summary and Rationale for Changes
Version 1.3 21 Feb. 2022	▪ Descriptions in '2.2 Background', '2.3. Benefit/Risk Assessment' and '4.3 Justification for Dose' have been updated ▪ Follow-up and end of study visits for participants who requested to discontinue from the study for receiving a booster dose of other available COVID-19 vaccine have been defined ▪ The actual enrolment status has been reflected in the consistency assessment between ethnicities ▪ pIMD list has been updated
Version 1.2 03 Sep. 2021	▪ Descriptions in '2.3.1. Risk Assessment' and '4.3 Justification for Dose' have been updated ▪ Updates on contraindications of the comparator vaccine have been reflected in '5.2. Exclusion Criteria' ▪ The rapid antibody kit test against SARS-CoV-2 has been replaced with the in vitro qualitative immunoassay ▪ '8.4.10. Unscheduled Visit' have been added for clarification
Version 1.1 21 Jul. 2021	▪ The post-vaccination timepoint for assessment of co-primary endpoints has been revised (4 weeks → 2 weeks post 2nd vaccination) ▪ The type of assays to analyze wild-type virus neutralizing antibodies and CMI responses, and related specimen collection timepoints have been revised ▪ The randomization ratios for Cohort 1 and 2 have been revised, thus the sample sizes have been adjusted accordingly ▪ GBP510 Phase 1 primary results have been updated ▪ Screening period has been shortened ▪ Sample size calculation has been updated based on the GBP510 Phase 1 immunogenicity result
Version 1.0 22 Jun. 2021	NA

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title: A Phase III, Randomized, Active-controlled, Observer-blind, Parallel-group, Multi-center Study to Assess the Immunogenicity and Safety of SK SARS-CoV-2 Recombinant Protein Nanoparticle Vaccine adjuvanted with AS03 (GBP510) in Adults Aged 18 Years and Older

Brief Title: A Phase III Study to Assess the Immunogenicity and Safety of SK SARS-CoV-2 Recombinant Protein Nanoparticle Vaccine adjuvanted with AS03 (GBP510) in Adults **Aged 18 Years and Older**

Rationale: Since the first report of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in Wuhan, China in December 2019, COVID-19 has rapidly become a pandemic, and more than 328 million cases of COVID-19 including more than 5.5 million deaths have been reported from over 223 countries and territories around the world as of January 2022.

Currently, ten vaccines have been listed by the WHO in Emergency Use Listing (EUL) (Pfizer/BioNTech, Moderna, Oxford/AstraZeneca, Serum Institute of India(Covishield, Covovax), Janssen, Beijing Institute of Biological Products, Sinovac, Bharat Biotech and Novavax). However, due to the global shortage and uneven supply of vaccines by countries, sufficient vaccines have not yet been secured to cover all the world's population, and further vaccine development is needed considering the emergence of variants of concern.

Given that National vaccination campaigns are being carried out targeting first high-risk groups and gradually expanding to the broader population, as well as the rate of prior COVID-19 infection in the population mean that efficacy clinical trials with placebo control are not only difficult to conduct practically, but also ethically questionable. Correlates of protection (CoP) based on antibody levels or functional activity have not yet been established, but all COVID-19 vaccine studies having reported vaccine efficacy have shown a robust correlation between antibody responses (i.e., neutralizing antibody and binding antibody) and vaccine efficacy despite geographically diverse study population, and use of different endpoints, assays and manufacturing platforms.[1]

Hence this study intends to "immune-bridge" the efficacy of GBP510 through an evaluation of superiority of immunogenicity compared to an active comparator (ChAdOx1-S [recombinant] AstraZeneca AB) which demonstrated clinical efficacy against COVID-19.

Objectives and Endpoints:

Primary Endpoints (Immunogenicity)	
Objectives	**Endpoints**

▪ To demonstrate that the immune response induced by 2 doses of GBP510 25µg adjuvanted with AS03 at 4-week interval in seronegative adults aged 18 years and older is superior / non-inferior to the immune response induced by 2 doses of ChAdOx1-S	For all participants of Cohort 1; ▪ (For superiority) GMT of neutralizing antibody to the SARS-CoV-2 measured by wild-type virus neutralization assays 2 weeks post 2nd vaccination ▪ (For non-inferiority) Percentage of participants with ≥ 4-fold rise in wild-type virus neutralizing antibody titre from baseline to 2 weeks post 2nd vaccination
Secondary Endpoints (Immunogenicity)	
Objectives	**Endpoints**
▪ To assess and compare the immune responses induced by 1 or 2 doses of GBP510 with ChAdOx1-S in seronegative adults aged 18 years and older ▪ To assess and compare the immune responses induced by 1 or 2 doses of GBP510 with ChAdOx1-S in seronegative adults aged 18 through 64 years ▪ To assess and compare the immune responses induced by 1 or 2 doses GBP510 with ChAdOx1-S in seronegative adults aged 65 years and older	Only in all participants of Cohort 1 at the following time points after study vaccination: 4 weeks post 1st vaccination; 2 weeks, 4 weeks, 6 months, and 12 months post 2nd vaccination ▪ GMT of SARS-CoV-2 RBD-binding IgG antibody measured by ELISA at each time point post-vaccination ▪ GMFR of SARS-CoV-2 RBD-binding IgG antibody measured by ELISA from baseline to each subsequent time point post-vaccination ▪ Percentage of participants with ≥ 4-fold rise in ELISA SARS-CoV-2 RBD-binding IgG titre from baseline to each subsequent time point post-vaccination ▪ GMT of neutralizing antibody to the SARS-CoV-2 measured by wild-type virus neutralization assays at each time point post-vaccination ▪ GMFR of neutralizing antibody to the SARS-CoV-2 measured by wild-type virus neutralization assays from baseline to each subsequent time point post-vaccination ▪ Percentage of participants with ≥ 4-fold rise in wild-type virus neutralizing antibody titre from baseline to each subsequent time point post-vaccination Only in a subset of 10% participants of Cohort 1 at the following time points after study vaccination: 2 weeks, 6 months, and 12 months post 2nd vaccination

	▪ Cell-mediated response for both Th1 and Th2 cytokines (including but not limited to INF-γ, TNF-α, IL-2, and IL-4 produced by T lymphocytes) measured by ELISpot / FluoroSpot, and for both CD4+ and CD8+ T-cells measured by FACS
Secondary Endpoints (Safety)	
Objectives	**Endpoints**
▪ To assess the safety profile of GBP510 in adults aged 18 years and older regardless of serostatus at baseline	In participants of all cohorts (Cohort 1+2); ▪ Occurrence of immediate systemic reactions in the 30 minutes post each vaccination ▪ Occurrence of solicited local AEs during 7 days post each vaccination ▪ Occurrence of solicited systemic AEs during 7 days post each vaccination ▪ Occurrence of unsolicited AEs during 28 days post each vaccination ▪ Occurrence of SAEs, MAAEs, AEs leading to study withdrawal, and AESIs during the whole study period
Exploratory Endpoints	
Objectives	**Endpoints**
▪ To describe the immune responses induced in adults aged 18 years and older who proved to be seropositive prior to study vaccination and/or to be infected during the study ▪ To describe the immune responses against the circulating strains, including the variants of concern ▪ To compare the incidence rates of virologically-confirmed COVID-19 between GBP510 and ChAdOx1-S ▪ To describe the consistency of immunogenicity across ethnicities ▪ To conduct other exploratory studies on samples collected from study participants to further evaluate the safety and/or immunogenicity profile of GBP510	

Overall Design:

This is a Phase III, randomized, active-controlled, observer-blind, parallel-group, multi-center study to compare the immunogenicity and safety of SK SARS-CoV-2 recombinant protein nanoparticle vaccine adjuvanted with AS03 (GBP510) to ChAdOx1-S in adults aged 18 years and older.

Approximately 1,950 adults with no history of SARS-CoV-2 infection and COVID-19 vaccination confirmed by a SARS-CoV-2 rapid antibody kit at screening will be enrolled in Cohort 1 (Immunogenicity Cohort), and another 2,040 adults will be enrolled in Cohort 2 (Safety Cohort) regardless of their serostatus. Approximately 20% of the participants will be the elderly population aged 65 years and older.

Cohort 1 (Immunogenicity Cohort):

Approximately 1,950 participants aged 18 years and older will be assigned to Cohort 1, and block-randomized in 2:1 ratio to receive 2 doses of either GBP510 (Test Vaccine) or ChAdOx1-S (Control Vaccine) at 4-week interval.

Cohort 2 (Safety Cohort):

Approximately 2,040 participants aged 18 years and older will be assigned to Cohort 2, and block-randomized in 5:1 ratio to receive 2 doses of GBP510 (Test Vaccine) or ChAdOx1-S (Control Vaccine) at 4-week interval.

Over the study period, all participants will attend 9 planned visits including telephone calls made 7 days after each vaccination (Day 7+3 after Visit 2 and Visit 4). Safety evaluations will equally be performed for all participants in Cohort 1 and 2, but blood samples for immunogenicity assessments will only be collected from the participants in Cohort 1. All participants in Cohort 1 will provide serum samples at baseline (Visit 2), 4 weeks after the 1st vaccination, and 2 weeks, 4 weeks, 6 months, and 12 months after the 2nd vaccination (Visit 4, 6, 7, 8, and 9) for ELISA and neutralization assays. The whole blood samples for assessment of cell-mediated immunity (CMI) will be collected at baseline (Visit 2), and 2 weeks, 6 months, and 12 months after the 2nd vaccination (Visit 6, 8, 9) only from a subset of approximately 10% participants who are pragmatically selected in advance retaining equal distribution between the Test and Control groups and age strata.

Cohort 1 Sample Size per Immunogenicity Analysis Method and Age groups

	ELISA / Wild-type virus neutralization assay (wtVNA): All participants in Cohort 1	CMI: Subset of 10% participants in Cohort 1
Test group (GBP510)		
All ages	1,300	130

18-64 years	1,040	104
≥ 65 years	260	26
Control group (ChAdOx1-S)		
All ages	650	65
18-64 years	520	52
≥ 65 years	130	13

Study vaccination will comprise 2 intramuscular injections of Test Vaccine (GBP510) or Control Vaccine (ChAdOx1-S) in an injection volume of approximately 0.5mL. The study vaccines will be injected into the deltoid muscle, preferably of the non-dominant arm at a 28-day interval. Alternative injection sites such as the hip or thigh may be used if an injection cannot be given in the deltoid muscle due to any medical conditions.

Brief Summary: The purpose of this study is to assess the immunogenicity and safety of SK SARS-CoV-2 recombinant protein nanoparticle vaccine adjuvanted with AS03 (GBP510) in adults aged 18 years and older.

Number of Participants:

Cohort 1 and 2 will comprise approximately 1,950 and 2,040 adult participants each.

Cohort	Treatment Group	Formulation	N (Elderly)
Cohort 1 (Immunogenicity cohort)	Test group (GBP510)	SK SARS-CoV-2 recombinant protein nanoparticle vaccine (RBD 25ug/dose) adjuvanted with AS03 (0.25ml); a total injection volume of 0.5mL	1,300 (260)
	Control group (ChAdOx1-S)	Chimpanzee Adenovirus encoding the SARS-CoV-2 Spike glycoprotein ChAdOx1-S, not less than 2.5×10^8 infectious units / 0.5mL	650 (130)
Cohort 2 (Safety cohort)	Test group (GBP510)	SK SARS-CoV-2 recombinant protein nanoparticle vaccine (RBD 25ug/dose) adjuvanted with AS03 (0.25ml); a total injection volume of 0.5mL	1,700 (340)

	Control group (ChAdOx1-S)	Chimpanzee Adenovirus encoding the SARS-CoV-2 Spike glycoprotein ChAdOx1-S, not less than 2.5×10^8 infectious units / 0.5mL	340 (68)

Intervention Groups and Duration:

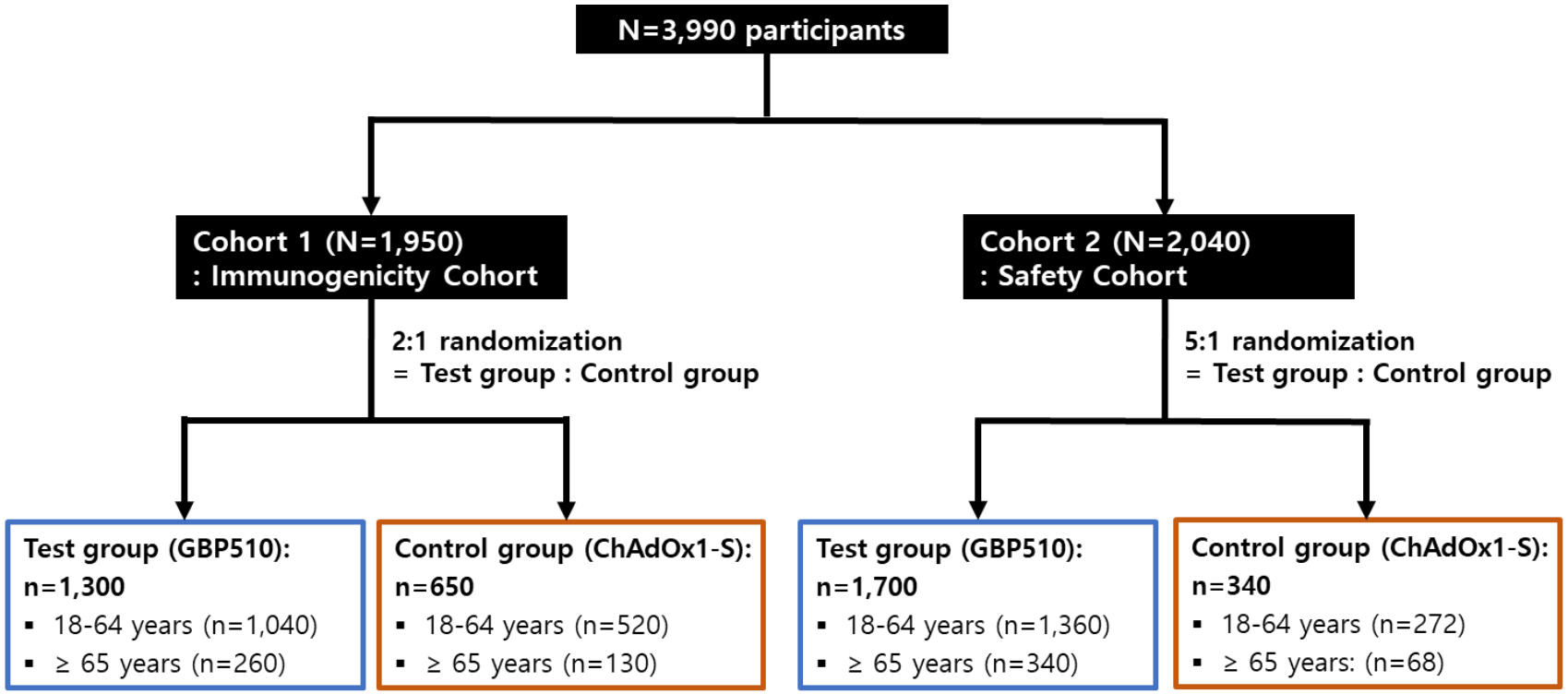
This study includes 2-dose schedule (28-day interval) of GBP510 and ChAdOx1-S.

Participants are expected to participate for up to a maximum of approximately 13 months. A 12-month study follow-up after the 2nd vaccination will be conducted.

Data Monitoring/Other Committee

An independent DSMB will be organized before study initiation. The DSMB will review accumulating blinded and unblinded safety data on a regular basis during the study period, and may recommend continuing study without modification, stopping further enrollment and vaccination, or considering changes or modification in study design. An unblinded review by the DSMB will also be performed as halting rules are met, or any safety concerns arise during this study.

1.2. Schema



*** Approximately 20% of the participants in each treatment group will be the elderly population aged ≥ 65 years**

1.3. Schedule of Activities (SoA)

The SoA table provides an overview of protocol visits and procedures.

Visit	Visit 1[$]	Visit 2[$]	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Unscheduled[@]
Visit description	**Screening**	**Vaccination 1**	**1-week Follow up (Telephone Contact)**	**Vaccination 2**	**1-week Follow up (Telephone Contact)**	**2-week Follow up**	**4-week Follow up**	**6-month Follow up**	**12-month Follow up**	
Visit windows (days)	**0 to 14 days Before Visit 2**	**Day 0**	**Day 7+3 after Visit 2**	**Day 28+5 After Visit 2**	**Day 7+3 after Visit 4**	**Day 14+3 after Visit 4**	**Day 28+5 after Visit 4**	**Day 168±14 after Visit 4**	**Day 365±14 after Visit 4**	
Informed consent	X									
Allocation of participant number	X									
Demographics	X									
Vital signs	X	X[†]		X[†]		X	X	X	X	X
Urine or serum pregnancy test (if applicable)	X	X[†]		X[†]				X		X
Physical examination[%]	X	X[†]		X[†]		X	X	X	X	X
Medical History	X[*]	X[†]								
Prior and concomitant medications	X[**]	X[†]	X	X[†]	X	X	X	X[***]	X[***]	X
Qualitative rapid kit test of SARS-CoV-2 antibody	X (a few drops of blood)									
Immunoassay for the in vitro qualitative detection of antibodies to SARS-CoV-2						SR03 (3.5mL)				
Inclusion/exclusion criteria	X	X[†]								

Obtain randomization number and study intervention allocation		X[†]								
Blood sampling for SARS-CoV-2 immunogenicity (ELISA, NAb)[#]		SR01[†] (10mL)		SR02[†] (10mL)		SR04 (10mL)	SR05 (10mL)	SR06 (10mL)	SR07 (10mL)	X
Blood sampling for SARS-CoV-2 immunogenicity (CMI)[#]: Only for the participants randomly selected		WB01[†] (32mL)				WB02 (32mL)		WB03 (32mL)	WB04 (32mL)	X
Study Vaccination		X		X						
Immediate Adverse Reaction (30 minutes monitoring post-vaccination)		X		X						
Provide and explain participant diary completion methods		X (1st diary)		X (2nd diary)			X (3rd diary)			X
Provide the participant with thermometer and rulers		X								
Review participant diary				X[&]		X[&]	X[&]	X[&]	X[&]	X
Collect participant diary				X (1st diary)			X (2nd diary)		X (3rd diary)	X
Collect solicited local and systemic AEs		X	X	X	X					X
Collect unsolicited AEs		X	X	X	X	X	X			X
Collect SAE, MAAE, AEs leading to study withdrawal, and AESI		X	X	X	X	X	X	X	X	X
Collect COVID-19 related information		X	X	X	X	X	X	X	X	X

[$] Visit 1(Screening) and Visit 2 may be conducted on the same day if all feasibility test results are available

[#] Blood samples for immunogenicity assessments will only be collected from the participants in Cohort 1

[%] A full physical examination will be performed at screening, and symptom-directed physical examinations will be followed for the subsequent visits

† Mandatory before vaccination.

& The participant will be asked to bring the diary with them as he or she returns to the site for Visit 4 and 6 to 9. Site staff should remind the participant to keep recording the diary during the visits.

* Clinically significant medical history within 14 days prior to screening will be obtained

** Prior and concomitant medications and vaccinations taken from 14 days prior to screening will be obtained

*** Any medications that are administered for treatment of SAE, MAAE, or AESI (including pIMDs) may be collected

@ Activities to be performed in unscheduled visits are optional, and can be chosen at the investigator's discretion

2. Introduction

2.1. Study Rationale

The purpose of developing GBP510 vaccine is to provide a wide coverage against COVID-19, particularly in LMIC settings. The GBP510 vaccine is a self-assembling recombinant protein subunit nanoparticle vaccine displaying SARS-CoV-2 spike receptor-binding domains (RBDs), and can be stored at regular refrigerator temperatures (2-8 ℃), making it suitable for rollout in parts of the world where ultracold storage is challenging.
The aim of this study is to assess the safety and immunogenicity of GBP510 for prevention of COVID-19, based on assumption that neutralizing antibody titre can reasonably predict efficacy. Correlates of protection (CoP) based on antibody levels or functional activity have not yet been established, but as the relationship between efficacy and in vitro neutralizing and binding antibodies of 7 licensed vaccines was assessed, a robust correlation was seen between neutralizing titre and efficacy (ρ= 0.79) and binding antibody titre and efficacy (ρ = 0.93), despite geographically diverse study populations, and use of different endpoints, assays, convalescent sera panels and manufacturing platforms.[1][2]

2.2. Background

Since the first report of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in Wuhan, China in December 2019, more than 328 million cases of COVID-19 including 5.5 million deaths have been reported from over 223 countries and territories around the world as of January 2022.[3][4]

Patients infected by SARS-CoV-2 mostly show mild or no symptoms. However, serious illnesses or deaths may occur especially in elderly patients, and the people with underlying medical conditions. Even though it is possible to recover from this infection, COVID-19 causes lingering long-term health problems including organ failures, trouble breathing, fatigue, blood clotting, or additional viral and bacterial infections. Besides medical complications in infected individuals, COVID-19 pandemic has resulted in huge burdens on public healthcare resources. Under these circumstances, precautions such as practicing social distancing and vaccination are the best preventive measures to block the transmission of SARS-CoV-2, which causes an enormous socioeconomic impact.

Therefore, development and sufficient supply of COVID-19 vaccines are urgent and crucial to elicit individual and herd immunity to prevent the transmission of SARS-CoV-2. Currently, ten vaccines have been listed by the WHO in EUL (Pfizer/BioNTech, Moderna, Oxford/AstraZeneca, Serum Institute of India(Covishield, Covovax), Janssen, Beijing Institute of Biological Products, Sinovac, Bharat Biotech and Novavax).[5] However, due to the global shortage and uneven supply of vaccines by countries, sufficient vaccines have not yet been secured to cover all the world's population, and further vaccine development is needed considering the emergence of variants of concern.

Among the different platform technologies that are being used for the development of COVID-19 vaccines, the recombinant protein vaccine platform allows the effective and rapid vaccine production and there are many commercialized vaccine products that are based on recombinant protein vaccine technology with demonstrated acceptable safety profile and product stability. SK bioscience has developed a novel nanoparticle vaccine candidate targeting the receptor

binding domain (RBD) of SARS-CoV-2 Spike protein. The candidate vaccine contains self-assembling, two-component nanoparticle (RBD-16GS-I53-50) that was developed by the Institute for Protein Design (IPD) at University of Washington (UW) using its structure-based vaccine design techniques. Also, AS03 developed by GlaxoSmithKline was used together with the candidate vaccine as an adjuvant. The candidate vaccine is expected to have an enhanced ability to provoke an immune response owing to its molecular structure enabling multivalent antigen presentation and it would allow affordable market access due to its high productivity in mammalian cells.

Clinical Summary

Two phase 1/2 studies (GBP510_001, GBP510_002) are being conducted in Korea by SK bioscience. These are 2-Stage, placebo-controlled, randomized, observer-blinded, dose-finding studies to assess the safety, reactogenicity, and immunogenicity of GBP510 vaccine adjuvanted with aluminum hydroxide or AS03 at 2 dose levels (10μg and 25μg).
A total of 260 and 320 healthy younger and older adults were enrolled and block-randomized respectively in 2:1 ratio for both Stage 1 (within each dose-level cohort) and Stage 2 to receive 2 doses of either one GBP510 formulation or placebo saline at a 28-day interval.
In Stage 1, each dose-level cohort comprised 30 and 40 adult participants aged between 19 and 55 years respectively for GBP510_001 and GBP510_002 studies. Further enrollment of 200 and 248 healthy younger and older adults aged 19 to 85 years in Stage 2 has also completed to date.
GBP510_002 study, originally designed as 2-Stage, was extended as 3-Stage and was approved by MFDS in November 2021. Stage 3 has been added to assess the safety, reactogenicity, and immunogenicity of GBP510 booster dose. A maximum of 100 participants who were previously randomized to Test group 3 (GBP510 25μg adjuvanted with AS03) in Stage 1 or 2 will be enrolled for Stage 3, to receive a third dose of GBP510 25μg adjuvanted with AS03.

The primary safety and immunogenicity analysis data from Stage 1 and a partial safety data accumulated by 14 days post-2nd vaccination in Stage 2 was available prior to the initiation of vaccination in this phase 3 study.

2.3. Benefit/Risk Assessment

2.3.1. Risk Assessment

The following potential risks related to the study vaccines have been identified, and it will be monitored during the study. More detailed information about the known and expected benefits and risks, reasonably expected adverse events, the potential risks, and uncertainties of the GBP510 vaccine may be found in the Investigator's Brochure (IB).

GBP510 Candidate Vaccine

SK bioscience GBP510 vaccine is a self-assembling protein nanoparticle vaccine displaying SARS-CoV-2 spike receptor-binding domains (RBDs).

Self-assembling or particulate protein immunogens are known as a clinically validated modality with a proven safety and efficacy data in humans. Self-assembling protein platforms for heterologous antigen

display have improved, and several protein nanoparticle vaccines displaying viral glycoprotein antigens are currently being evaluated in clinical trials.[6], [7], [8]

AS03 Adjuvant System

AS03 is an Adjuvant System containing a surfactant, polysorbate 80, and two biodegradable oils, α-tocopherol and squalene, in phosphate-buffered saline as the aqueous carrier. AS03 activates the innate immune response at the injection site which enhances adaptive immune responses to the vaccine antigen.

There is data from non-clinical studies on local tolerance, toxicology and safety pharmacology with AS03 administered alone or combined with various influenza antigens in animals, that did not identify any safety concern that would preclude the use of the adjuvant in clinical trials. Extensive safety data were collected from the clinical development programs of AS03-adjuvanted vaccines against different influenza subtypes and from post-licensure experience, including pharmacovigilance and safety studies of AS03-adjuvanted A/H1N1pdm09 vaccines. An increased risk of narcolepsy was observed in some individuals after the vaccination campaign with Pandemrix™ in 2009-2010. A similar risk of narcolepsy was not identified with other non-adjuvanted influenza vaccines or other AS03-adjuvanted vaccines, like Arepanrix™ [Montplaisir 2014, Cohet 2015]. Current data suggest that cases of narcolepsy seen immediately following the 2009-2010 pandemic were most likely the result of an immune cascade, triggered by CD4 T cell cross-reactivity to HA proteins from the H1N1 virus itself and hypocretin. Research is continuing to assess whether either of the main components of the 2009/2010 flu pandemic vaccine (e.g., the viral proteins in the form used in the vaccine or the AS03 adjuvant) may have contributed to the reaction. Otherwise, it has been shown that AS03-adjuvanted influenza vaccines were generally well tolerated and displayed an acceptable safety profile.[9]

However, based on the theoretical concern that vaccination with an adjuvanted vaccine containing potent immunostimulants may interfere with immunological self-tolerance, potential immune mediated disorders (pIMDs) will be included and monitored as adverse events of special interest (AESI) during this study period. pIMDs are a subset of AEs that include autoimmune diseases and other inflammatory and/or neurological disorders of interest which may or may not have an autoimmune etiology. During the informed consent process, the participants enrolling in the study will be informed of this potential risk and the need to attend the clinic if they are unwell.

Nonclinical Data on GBP510 Candidate Vaccine

Immunogenicity: Immunogenicity of AS03 adjuvanted GBP510 was evaluated by using BALB/c mice. Vaccination was proceeded twice with a 3-week interval, and serum was collected two and five weeks after the first immunization. AS03 adjuvanted GBP510 appeared to induce higher RBD-specific IgG and neutralizing antibodies. Furthermore, immunized mice also showed higher induction of RBD-specific T cells secreting either IFN-γ or IL-4, indicating that AS03 adjuvanted GBP510 induced cellular mediated immune response.

To further assess the efficacy of AS03 adjuvanted GBP510, hACE2 transgenic mice were vaccinated twice with a 3-week interval and infected with SARS-CoV-2, 6 weeks after the first vaccination. In addition to the original strain, UK (B.1.1.7) and SA (B.1.351) variants were also used to evaluate the cross-reactivity of AS03 adjuvanted GBP510. All unvaccinated mice developed weight loss and eventually succumbed to SARS-CoV-2, while vaccinated mice appeared healthy. Neutralizing antibodies against original and variant strains of SARS-CoV-2 were also higher in vaccinated TG mice, proving the protective effect and cross-reactivity of AS03 adjuvanted GBP510.

In addition to the mouse study, Cynomolgus macaques were used for NHP study to evaluate immunogenicity and protective effect of AS03 adjuvanted GBP510 against SARS-CoV-2. Vaccination was proceeded twice with a 3-week interval, and serum was collected three and six weeks after the first immunization. The titre of RBD-specific IgG antibodies and RBD-specific T cells secreting either IFN-γ or IL-4 were higher in the immunized NHPs, showing the immunogenic effect of AS03 adjuvanted GBP510. For the evaluation of cross-reactivity of AS03 adjuvanted GBP510, neutralizing antibodies against original, UK, SA and BR (P1) strains were measured. Results showed higher titres of neutralizing antibodies against original and all variant strains of SARS-CoV-2 in immunized NHPs, indicating the cross-reactivity of AS03 adjuvanted GBP510. To evaluate protection against infection, NHPs were challenged with SARS-CoV-2, 7 weeks after the first immunization, and nose and throat swabs were collected 7 days after the infection to measure viral load. Results showed that viral load in both nose and throat was lower and lasted shorter in the immunized NHPs, proving the protective effect of AS03 adjuvanted GBP510 against SARS-CoV-2.

Taken together, it can be concluded that GBP510 vaccine adjuvanted with AS03 have immunogenic and protective effects against SARS-CoV-2 in mice and NHPs. This was not limited to the original strain, but was also feasible against variant strains. In addition, no adverse effect related to the vaccine was found during all tests, eliciting the potential of the AS03 adjuvanted GBP510 as a safe and effective vaccine candidate.

Nonclinical Study: In the multiple dose toxicity study, the potential systemic toxicity and local tolerance to AS03 adjuvanted GBP510 candidate vaccine were evaluated following multiple intramuscular administration to Sprague-Dawley Rats. The changes observed during the study were limited to some transient changes, which is consistent with mild inflammatory response and an immune stimulation associated with administration of a vaccine.

In another multiple dose toxicity study, Sprague-Dawley Rats were vaccinated three times (intervals of 2 weeks) at a dose of 30μg(0.5mL). Toxicologically harmful changes were not observed in terms of systemic toxicity, followed-up by 4 weeks after 3rd vaccination.

When vaccinating Sprague-Dawley Rats four times at a dose of 24μg (0.2mL), there were no systemically toxic adverse findings as well, followed-up by 4 weeks after 4th vaccination.

In the developmental and reproductive toxicity study of AS03 adjuvanted GBP510 candidate vaccine, there were no maternal reproductive toxicity and pre-/post-natal development toxicity (until weaning) in AS03 adjuvanted GBP510 candidate vaccine in SD rats.

In the safety pharmacology studies (core-battery studies) of AS03 adjuvanted GBP510 candidate vaccine, it did not affect the central nervous system of SD rats, the respiratory system of SD rats and the cardiovascular system of Beagle dogs. To evaluate the transient changes of the respiratory system, AS03 adjuvanted GBP510 candidate vaccine was additionally measured its potential effect for up to 48 hours, when it was normalized at.

Clinical Data on GBP510 Candidate Vaccine

The primary safety data from the healthy 328 adults in the Stage 1 & 2 of phase 1/2 study (protocol no.: GBP510_002) is available. Of 328 individuals in the ITT set, 101 participants were enrolled to GBP510 10μg adjuvanted with AS03(Test group 1), 10 participants to GBP510 10μg (Test group 2), 104 participants to GBP510 25μg adjuvanted with AS03(Test group 3), 52 participants to GBP510 25μg (Test group 4) and 61 participants to Placebo group.

RBD-binding IgG titres and SARS-CoV-2-neutralizing titres were assessed at baseline, at 4 weeks post-1st study vaccination, at 2 weeks and 4 weeks post-2nd study vaccination. Geometric mean titres peaked by 2 weeks in all dose groups that received two doses of study vaccine, and significantly greater serum IgG and neutralizing GMTs were achieved 2 weeks post-2nd vaccination of GBP510 low- and high-dose adjuvanted with AS03. The neutralizing GMTs assessed by PBNA 2 weeks post-2nd vaccination of two adjuvanted groups were 5.7-fold and 6.0-fold the GMT of the NIBSC reference HCS panel, respectively. The adjuvanted GBP510 groups have shown to induce RBD-specific CD4+ T-cell cytokine responses with a predominant Th1 profile.

Of 327 individuals in the Safety Set, there was no immediate systemic AE after any vaccine injection in all treatment groups. Injection site pain was the most common Solicited Local AEs within 7 days after each study vaccination (85.58% after each vaccination in Test group 3) and the other Solicited Local AEs (Injection site redness, Injection site swelling) rarely occurred after each study vaccination in Test groups (2.88% and 9.62% for Injection site redness, 10.58% and 7.69% for Injection site swelling after first and second dose in Test group 3). Most Solicited Local AEs were mild and moderate in severity after the first dose, but more moderate and severe cases occurred after the second dose. Solicited Local AEs were resolved within a mean of less than 4 days

Fatigue, Headache, and Myalgia were the most frequent Solicited Systemic AEs (75.00%, 56.73%, 79.81% after any doses in Test group 3), and the incidence of most Solicited Systemic AEs showed a tendency to increase after the second dose. Most Solicited Systemic AEs were mild and moderate in severity after the first dose, but more moderate and severe cases occurred after the second dose. Grade 3 (Severe) Solicited Systemic AE occurred 6 cases in Test group 1, 16 cases in Test group 3, all occurring after the 2nd vaccination. All severe cases resolved within 8 days of onset.

Solicited AEs were reported more frequently in young adults aged 19 - 64 years than the elderly aged 65 years or older, the reactogenicity profile were consistent between the age subgroups.

As of Jan, 2022, 8 serious adverse events (deterioration of hemorrhoids, left breast cancer, 2 cases of hospitalization due to traffic accidents, ovarian cancer, acute appendicitis, left ureter and both kidney stone and spontaneous abortion) have been reported from 328 participants in the Phase 1/2 study, and

none of which were considered related to study vaccine as assessed by the investigators. Adverse event of special interest including potential immune-mediate diseases have not occurred.

Control Vaccine (ChAdOx1-S)[10], [11]

The most common side effects with ChAdOx1-S in the trials were usually mild or moderate and got better within a few days after vaccination. The most common side effects are tenderness, pain and bruising at the injection site, headache, tiredness, muscle pain, general feeling of being unwell, chills, fever, joint pain and nausea. They affected more than 1 in 10 people.

Thrombocytopenia (low levels of blood platelets), vomiting, diarrhoea, swelling and redness at the injection site occurred in less than 1 in 10 people. Lymphadenopathy (enlarged lymph nodes), decreased appetite, dizziness, sleepiness, sweating, abdominal (belly) pain, itching and rash occurred in less than 1 in 100 people.

Allergic reactions have occurred in people receiving the vaccine, including some cases of severe allergic reactions (anaphylaxis). Appropriate medical treatment and supervision will always be readily available in case of an anaphylactic event following the administration of the vaccine. Close observation for at least 30 minutes will be conducted following vaccination. A second dose of the study vaccine will not be given to those who have experienced anaphylaxis to the first dose of study vaccine.

Thrombosis (formation of blood clots in the blood vessels) in combination with thrombocytopenia (thrombosis with thrombocytopenia syndrome, TTS) occurred in less than 1 in 10,000 people. TTS, in some cases accompanied by bleeding, has been observed very rarely following vaccination with ChAdOx1-S. This includes severe cases presenting as venous thrombosis, including unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis, concomitant with thrombocytopenia. Some cases had a fatal outcome. The majority of these cases occurred within the first three weeks following vaccination and occurred mostly in women under 60 years of age. Participants will be instructed to seek immediate medical attention if they develop symptoms such as shortness of breath, chest pain, leg swelling, leg pain, persistent abdominal pain following study vaccination. Additionally, anyone with neurological symptoms including severe or persistent headaches, blurred vision, confusion or seizures after vaccination, or who experiences skin bruising (petechia) beyond the site of vaccination after a few days, should seek prompt medical attention. Participants diagnosed with thrombocytopenia within three weeks after vaccination with ChAdOx1-S, will be actively investigated for signs of thrombosis. Similarly, participants who present with thrombosis within three weeks of vaccination will be evaluated for thrombocytopenia. Investigators may consult applicable guidance and/or specialists (e.g., haematologists, specialists in coagulation) to diagnose and treat this condition.

Very rare cases of capillary leak syndrome (CLS) have also been reported in the first days after vaccination with ChAdOx1-S. A history of CLS was apparent in some of the cases and fatal outcome has been reported. CLS is a rare disorder characterized by acute episodes of oedema mainly affecting the limbs, hypotension, haemoconcentration and hypoalbuminaemia. Participants with an acute episode of CLS following study vaccination require prompt recognition and treatment. Intensive supportive therapy

is usually warranted. Participants with a known history of CLS should not be vaccinated with the study vaccine

A second dose of the study vaccine will not be given to the participant who has had TTS or CLS after receiving the first study vaccine.

General Risks Related to Vaccination and Blood Draw

Vaccination or drawing blood may cause syncope (fainting) as a psychogenic response to the needle injection. Procedures will be in place to prevent falling injury and manage syncopal reactions. Also, as with any vaccine, immediate and potentially life-threatening allergic reactions to the vaccine could be manifested by AEs such as laryngeal edema, asthma, urticaria, rash, hypotension, and anaphylaxis. However, these types of reactions are very rare. Appropriate medical equipment and emergency medications, including epinephrine (1:1000), should be available on trial site in the event of an anaphylactic, vasovagal, or other immediate allergic reaction.

2.3.2. Benefit Assessment

Some of participants assigned in Control group will receive 2 doses of ChAdOx1-S for which sufficient efficacy and safety data have been generated and is currently used by many countries for COVID-19 Emergency Use Authorization.[16]

The efficacy or immunogenicity of GBP510 vaccine has yet to be established, thus the overall benefit and risk balance for participants assigned in Test group was ascertained based on accumulated phase 1/2 study results.

Participants may benefit from a variety of clinical testing and physical examination scheduled in this study.

3. Objectives and Endpoints

Primary Endpoints (Immunogenicity)	
Objectives	**Endpoints**
▪ To demonstrate that the immune response induced by 2 doses of GBP510 25µg adjuvanted to AS03 at 4-week interval in seronegative adults aged 18 years and older is superior / non-inferior to the immune response induced by 2 doses of ChAdOx1-S	For all participants of Cohort 1; ▪ (For superiority) GMT of neutralizing antibody to the SARS-CoV-2 measured by wild-type virus neutralization assays 2 weeks post 2nd vaccination ▪ (For non-inferiority) Percentage of participants with ≥ 4-fold rise in wild-type virus neutralizing antibody titre from baseline to 2 weeks post 2nd vaccination
Secondary Endpoints (Immunogenicity)	
Objectives	**Endpoints**
▪ To assess and compare the immune responses induced by 1 or 2 doses of GBP510 with ChAdOx1-S in seronegative adults aged 18 years and older ▪ To assess and compare the immune responses induced by 1 or 2 doses of GBP510 with ChAdOx1-S in seronegative adults aged 18 through 64 years ▪ To assess and compare the immune responses induced by 1 or 2 doses GBP510 with ChAdOx1-S in seronegative adults aged 65 years and older	Only in all participants of Cohort 1 at the following time points after study vaccination: 4 weeks post 1st vaccination; 2 weeks, 4 weeks, 6 months, and 12 months post 2nd vaccination ▪ GMT of SARS-CoV-2 RBD-binding IgG antibody measured by ELISA at each time point post-vaccination ▪ GMFR of SARS-CoV-2 RBD-binding IgG antibody measured by ELISA from baseline to each subsequent time point post-vaccination ▪ Percentage of participants with ≥ 4-fold rise in ELISA SARS-CoV-2 RBD-binding IgG titre from baseline to each subsequent time point post-vaccination ▪ GMT of neutralizing antibody to the SARS-CoV-2 measured by wild-type virus neutralization assays at each time point post-vaccination ▪ GMFR of neutralizing antibody to the SARS-CoV-2 measured by wild-type virus neutralization assays from baseline to each subsequent time point post-vaccination ▪ Percentage of participants with ≥ 4-fold rise in wild-type virus neutralizing antibody titre from baseline to each subsequent time point post-vaccination

	Only in a subset of 10% participants of Cohort 1 at the following partial time points after study vaccination: 2 weeks, 6 months, and 12 months post 2nd vaccination ▪ Cell-mediated response for both Th1 and Th2 cytokines (including but not limited to INF-γ, TNF-α, IL-2, and IL-4 produced by T lymphocytes) measured by ELISpot / FluoroSpot, and for both CD4+ and CD8+ T-cells measured by FACS
Secondary Endpoints (Safety)	
Objectives	**Endpoints**
▪ To assess the safety profile of GBP510 in adults aged 18 years and older regardless of serostatus at baseline	In participants of all cohorts (Cohort 1+2); ▪ Occurrence of immediate systemic reactions in the 30 minutes post each vaccination ▪ Occurrence of solicited local AEs during 7 days post each vaccination ▪ Occurrence of solicited systemic AEs during 7 days post each vaccination ▪ Occurrence of unsolicited AEs during 28 days post each vaccination ▪ Occurrence of SAEs, MAAEs, AEs leading to study withdrawal, and AESIs during the whole study period
Exploratory Endpoints	
Objectives	**Endpoints**
▪ To describe the immune responses induced in adults aged 18 years and older who proved to be seropositive prior to study vaccination and/or to be infected during the study ▪ To describe the immune responses against the circulating strains, including the variants of concern ▪ To compare the incidence rates of virologically-confirmed COVID-19 between GBP510 and ChAdOx1-S ▪ To describe the consistency of immunogenicity across ethnicities ▪ To conduct other exploratory studies on samples collected from study participants to further evaluate the	

safety and/or immunogenicity profile of GBP510	

4. Study Design

4.1. Overall Design

This is a Phase III, randomized, active-controlled, observer-blind, parallel-group, multi-center study to compare the immunogenicity and safety of SK SARS-CoV-2 recombinant protein nanoparticle vaccine adjuvanted with AS03 (GBP510) to ChAdOx1-S in adults aged 18 years and older.

Approximately 1,950 adults with no history of SARS-CoV-2 infection and COVID-19 vaccination confirmed by a SARS-CoV-2 rapid antibody kit at screening will be enrolled in Cohort 1 (Immunogenicity Cohort), and another 2,040 adults will be enrolled in Cohort 2 (Safety Cohort) regardless of their serostatus confirmed by a SARS-CoV-2 rapid antibody kit at screening. Approximately 20% of the participants will be elderly population aged 65 years and older (Table 1).

Cohort 1 (Immunogenicity cohort):

Approximately 1,950 participants aged 18 years and older will be assigned to Cohort 1, and block-randomized in 2:1 ratio to receive 2 doses of either GBP510 (Test Vaccine) or ChAdOx1-S (Control Vaccine) at 4-week interval.

Cohort 2 (Safety cohort):

Approximately 2,040 participants aged 18 years and older will be assigned to Cohort 2, and block-randomized in 5:1 ratio to receive 2 doses of GBP510 (Test Vaccine) or ChAdOx1-S (Control Vaccine) at 4-week interval.

Study vaccination will comprise 2 intramuscular injections of Test Vaccine (GBP510) or Control Vaccine (ChAdOx1-S) in an injection volume of approximately 0.5mL. The study vaccines will be injected into the deltoid muscle, preferably of the non-dominant arm at a 28-day interval. Alternative injection sites such as the hip or thigh may be used if an injection cannot be given in the deltoid muscle due to any medical conditions.

Table 1. Study Cohort / Treatment Group

Cohort	Treatment Group	Formulation	N (Elderly)
Cohort 1 (Immunogenicity cohort)	Test group (GBP510)	SK SARS-CoV-2 recombinant protein nanoparticle vaccine (RBD 25ug/dose) adjuvanted with AS03 (0.25mL); a total injection volume of 0.5mL	1,300 (260)

	Control group (ChAdOx1-S)	Chimpanzee Adenovirus encoding the SARS-CoV-2 Spike glycoprotein ChAdOx1-S, not less than 2.5 × 10^8infectious units / 0.5mL	650 (130)
Cohort 2 (Safety cohort)	Test group (GBP510)	SK SARS-CoV-2 recombinant protein nanoparticle vaccine (RBD 25ug/dose) adjuvanted with AS03 (0.25mL); a total injection volume of 0.5mL	1,700 (340)
	Control group (ChAdOx1-S)	Chimpanzee Adenovirus encoding the SARS-CoV-2 Spike glycoprotein ChAdOx1-S, not less than 2.5 × 10^8infectious units / 0.5mL	340 (68)

Over the study period, all participants will attend 9 planned visits including telephone calls made 7 days after each vaccination (Day 7+3 after Visit 2 and Visit 4). Safety evaluations will equally be performed for all participants in Cohort 1 and 2, but blood samples for immunogenicity assessments will only be collected from the participants in Cohort 1. All participants in Cohort 1 will provide serum samples at baseline (Visit 2), 4 weeks after the 1st vaccination, and 2 weeks, 4 weeks, 6 months, and 12 months after the 2nd vaccination (Visit 4, 6, 7, 8, and 9) for ELISA and neutralization assays. The whole blood samples for assessment of cell-mediated immunity (CMI) will be collected at baseline (Visit 2), and 2 weeks, 6 months, and 12 months after the 2nd vaccination (Visit 6, 8, 9) only from a subset of approximately 10% participants who are pragmatically selected in advance retaining equal distribution between the Test and Control groups and age strata.

Table 2. Cohort 1 Sample Size per Immunogenicity Analysis Method and Age Groups

	ELISA / Wild-type virus neutralization assay (wtVNA): All participants in Cohort 1	CMI: Subset of 10% participants in Cohort 1
Test group (GBP510)		
All ages	1,300	130
18-64 years	1,040	104
≥ 65 years	260	26
Control group (ChAdOx1-S)		
All ages	650	65
18-64 years	520	52
≥ 65 years	130	13

An independent DSMB will be organized before study initiation. The DSMB will review accumulating blinded and unblinded safety data on a regular basis during the study period, and may recommend continuing study without modification, stopping further enrollment and vaccination, or considering changes or modification in study design. An unblinded review by DSMB will be performed as halting rules are met, or any safety concerns arise during this study.

4.2. Scientific Rationale for Study Design

This study is designed as an active-controlled, randomized, observer-blinded, parallel-group study. Unblinded study staff will be assigned for preparation and administration of study intervention, since GBP510 and ChAdOx1-S are different in appearance. Additionally, an independent DSMB will be formed and allowed to review safety data in a blinded and unblinded manner, which will facilitate ongoing safety monitoring.

The maximum blood volume to be collected during the study period will comply with the US Department of Health and Human Services Office for Human Research Protections and US FDA guidelines, thus will not exceed 550 ml in an 8-week period and collection may not occur more frequently than 2 times per week.[12][13]

4.3. Justification for Dose

Based on the Phase 1 immunogenicity and safety data from 80 adults aged 19 to 55 years, higher GMT, GMFR, and seroconversion rates in ELISA and neutralization assays (PBNA) were observed in the group receiving two doses of GBP510 25μg-AS03 (20 adults) when compared to the non-adjuvanted groups and the group receiving GBP510 10μg-AS03. The overall immunogenic profile of GBP510 25μg-AS03 was most preferred given the longevity of immune response and protection against the variants of concern. GBP510 10μg-AS03 and 25μg-AS03 groups presented a similar incidence rate and severity of solicited local and systemic reactions, and no clinically significant concerns such as AESIs were identified. eight SAEs reported up to the present in GBP510_002 study were judged to be not related to study vaccine.

Therefore, the sponsor has determined to proceed with the two doses regimen of GBP510 25μg adjuvanted with AS03 in this Phase 3 study.

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. A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the Schedule of Activities.

5. Study Population

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

5.1. Inclusion Criteria

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

Age

1. Participant must be 18 years of age and older, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants who are healthy or medically stable as determined by medical evaluation including medical history, physical examination, clinical laboratory tests, and medical judgement of the investigator.
3. Participants who are able to attend all scheduled visits and comply with all study procedures.

Sex and Contraceptive/Barrier Requirements

4. Female participants of childbearing potential must agree to be heterosexually inactive, or agree to consistently use at least one acceptable method of contraception from at least 4 weeks prior to the 1st study vaccination to 12 weeks after the last study vaccination (See Section 5.3 for postmenopausal condition, and Appendix 10.3 for detailed contraceptive methods)
5. Female participants with a negative urine or serum pregnancy test at screening

   ** Female participants who are surgically sterile or postmenopausal with amenorrhea for at least 12 months are not subject for pregnancy test*

Informed Consent

6. Capable of giving signed informed consent as described in Appendix 10.1.3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions

1. Any clinically significant respiratory symptoms (e.g., cough, sore throat), febrile illness (tympanic temperature >38°C), or acute illness within 72 hours prior to the 1st study vaccination. A prospective participant should not be included until 72 hours after the condition has resolved.

2. (Only for Cohort 1) Prior SARS-CoV-2 infection or vaccination confirmed by a positive result of qualitative test for SARS-CoV-2 antibody using a rapid antibody kit at screening
3. History of virologically-confirmed SARS or MERS disease, or SARS / MERS vaccination
4. History of congenital, hereditary, acquired immunodeficiency, or autoimmune disease
5. History of bleeding disorder including thrombocytopenia which is contraindicating intramuscular vaccination
6. History of thrombosis, immune thrombocytopenia, or capillary leak syndrome which is contraindicating ChAdOx1-S vaccination
7. History of hypersensitivity and severe allergic reaction (e.g., anaphylaxis, Guillain-Barre syndrome) to any vaccines or components of the study vaccine
8. History of malignancy within 1 year prior to the 1st study vaccination (with the exception of malignancy with minimal risk of recurrence at the discretion of the investigator).
9. Significant unstable chronic or acute illness that, in the opinion of the investigator, might pose a health risk to the participant if enrolled, or could interfere with the protocol-specified activities, or interpretation of study results

   ** The summary of product characteristics for ChAdOx1-S, and the AESIs as outlined in Section 8.1.4 should be considered for evaluating the participant*
10. Any other conditions which, in the opinion of the investigator, might interfere with the evaluation of the study objectives (e.g., alcohol or drug abuse, neurologic or psychiatric conditions)
11. Female participants who are pregnant or breastfeeding

Prior / Concomitant Therapy

12. Receipt of any medications or vaccinations intended to prevent COVID-19
13. Receipt of any vaccine within 4 weeks prior to the 1st study vaccination or planned receipt of any vaccine from enrollment through 28 days after the last study vaccination (Visit 7), except for influenza vaccination, which may be received at least 2 weeks prior to the 1st study vaccination. This exception includes monovalent pandemic influenza vaccines and multivalent influenza vaccines
14. Receipt of immunoglobulins and/or any blood or blood products within 12 weeks prior to the 1st study vaccination
15. Chronic use (more than 2 consecutive weeks) of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy; or long-term systemic corticosteroid therapy (≥ 10mg prednisone/day or equivalent for more than 2 consecutive weeks) within 12 weeks prior to the 1st vaccination. The use of topical and nasal glucocorticoids will be permitted

Prior / Concurrent Clinical Study Experience

16. Participation in another clinical study involving study intervention within 4 weeks prior to the 1st study vaccination, or concurrent, planned participation in another clinical study with study intervention during the study period.

Other Exclusions

17. Participants who are subjected to any global or local restrictions in place for use of ChAdOx1-S (e.g. age, gender, or other specific population groups)
18. Investigators, or study staff who are directly involved in the conduct of this study or supervised by the investigator, and their respective family members.

5.3. Lifestyle Considerations

Female participants of childbearing potential

Female participants of childbearing potential must use an appropriate method of contraception from 4 weeks before 1st study vaccination and through 12 weeks after the last study vaccination. Female participants who are surgically sterile or postmenopausal with amenorrhea for at least 12 months will not be subject for use of contraception.

The investigator or designee record the selected contraception method and instruct the female participant of childbearing potential to contact the site staff if pregnancy is known or suspected.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study vaccine due to the inclusion/exclusion criteria. 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, eligibility criteria, and any SAE.

If a participant fails to meet the eligibility criteria for participation in this study due to a temporary condition (e.g., acute illness, fever), re-screening may be conducted after the condition had resolved under a different participant number.

5.5. Criteria for Temporarily Delaying

If a participant experiences the following conditions, the investigator may postpone study vaccination until 72 hours after the condition is resolved. The delay should still be within timeframe for study vaccination indicated in the SoA (Section 1.3).

- Any clinically significant respiratory symptoms (e.g., cough, sore throat), febrile illness (tympanic temperature >38°C), or acute illness within 72 hours prior to each study vaccination.

6. Study Intervention(s) and Concomitant Therapy

Study intervention is defined as any investigational intervention(s), intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

	Test drug	Comparator drug
Intervention Name	SARS-CoV-2 Recombinant Protein Nanoparticle Vaccine (GBP510)	ChAdOx1-S
Type	Vaccine	Vaccine
Dose Formulation	Multi-use vials, with an extractable volume of 5 mL	Multi-use vials, with an extractable volume of 4 or 5 mL
Unit Dose Strength(s)	GBP510 adjuvanted with AS03 (RBD of SARS-CoV-2 25ug / dose); a total injection volume of 0.5mL	5×10^{10} viral particles per dose corresponding to not less than 2.5×10^{8} infectious units
Dosage Level(s)	GBP510 (for mixing with AS03): SARS-CoV-2 RBD nanoparticle 25μg, per 0.25 mL AS03:0.25mL	One dose (0.5 ml) contains Chimpanzee Adenovirus encoding the SARS-CoV-2 Spike glycoprotein (ChAdOx1-S), not less than 2.5×10^{8} infectious units
Route of Administration	Intramuscular injection	Intramuscular injection
Dose Interval	2 doses at 4 weeks interval	2 doses at 4 weeks interval
Storage Condition	2~8℃	2~8℃
Use	Experimental	Experimental
IMP and NIMP	IMP	NIMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Study intervention will be provided in 2 multidose vials for 10 doses, each containing 3.1mL of GBP510 and 3.15mL of adjuvant (AS03) respectively. Packages will be labeled as required per country requirement	Study intervention will be provided in 10-dose (5mL) multidose vials within a carton. Each carton and vial will be labelled as required per country requirement

6.2. Preparation/Handling/Storage/Accountability

- The investigator or designee (i.e., unblinded study pharmacists) must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention. If any excursions or damage to the package is identified, site staff should immediately quarantine the study intervention, alert the sponsor or representative, provide temperature monitoring record and request authorization for use.
- The investigator or designee must confirm the appropriate labeling of study intervention according to local legal requirements.
- Only participants enrolled and randomized in the study may receive study intervention and only authorized site staff may administer study intervention. 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 the authorized site staff. Authorized site staff should maintain a temperature record to establish compliance with the storage conditions.
- The investigator or designee, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, dispensing, injections, and return to the sponsor or disposition records).
- Further guidance and information including the final disposition of used and unused study interventions are provided in the IP Manual.
- An unblinded site monitor will verify the accountability and storage records during site visits.

6.2.1. Labeling and Packaging

The study intervention is to be labeled and packed according to the applicable local regulation. Approximately 10 doses (SARS-CoV-2 RBD 25μg) of GBP510 will be dispatched in an antigen vial with one adjuvant vial containing AS03. The label will state “Investigational Product for clinical trial use only”.

The original packaging of ChAdOx1-S will be repacked, and the primary and secondary packages will have clinical labels.

6.2.2. Preparation and Dispensing

Study intervention should be dispensed by qualified unblinded site staff (i.e., study pharmacists) as allowed by local regulations. Accurate accountability records should be kept in regard to when and how much study intervention is dispensed for each participant.

6.2.3. Administration

Study vaccination will comprise 2 intramuscular injections of a GBP510 to be mixed with AS03 (25μg SARS-CoV-2 RBD; a total injection volume of 0.5mL) or ChAdOx1-S (Chimpanzee Adenovirus encoding the

SARS-CoV-2 Spike glycoprotein ChAdOx1-S, not less than 2.5×10^8 infectious units; a total injection volume of 0.5mL) at 4 weeks interval.

For reconstituting a GBP510 vaccine adjuvanted with AS03 at 1:1 ratio, the total volume of AS03 (approximately 3.1mL) will be withdrawn from an adjuvant vial, and put in another vial containing 3.1mL of GBP510 (SARS-CoV-2 RBD 25ug per dose). For each injection, 0.5mL will be withdrawn from a vial containing approximately 6.2mL of GBP510 mixed with AS03.

0.5mL of ChAdOx1-S will be withdrawn from a vial of 5mL into a syringe for injection.

For both GBP510 and ChAdOx1-S vaccines, the opened vial (punctured by a needle) can be stored up to 48 hours at temperatures between 2~8°C. During this refrigeration period, the opened vial may be kept and used within a single period of 6 hours at room temperatures up to 30°C, but the residual volume must be discarded after then.

Study intervention will be administered by qualified unblinded site personnel (i.e., unblinded study vaccinators) according to the IP Manual ensuring the participants remain blinded. Study intervention administration details should be recorded for each participant.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Randomization and Allocation Procedures

Trial sites will be priorly allocated to either Cohort 1 or 2, taking into account the respective number of participants planned for recruitment.

On the day of enrollment in a trial site assigned for Cohort 1, participants who meet the inclusion/exclusion criteria and signed the ICF will be randomly assigned to Test group / Control group in a 2:1 ratio to have approximatively 1,950 participants (1,300 participants in Test group, 650 participants in Control group). Another approximately 2,040 participants in the trial sites for Cohort 2 will be randomly assigned to Test group / Control group in a 5:1 ratio (1,700 participants in Test group, 340 participants in Control group).

The centralized IRT will be used to randomly allocate participant according to pre-generated blocked randomization schedules. The IRT will provide the treatment assignment and have the unblinded site staff confirm it. Randomization will be stratified by age (18-64 or ≥65 years) and trial site to pursue an approximately equal distribution of participants among the treatment groups within each age group and trial site.

6.3.2. Blinding

This study will be observer-blinded between GBP510 and ChAdOx1-S.

The participant, investigator and other study staff members including study coordinator who collect safety data, the sponsor, and laboratory personnel who conducts serology analysis, will not know which study intervention was administered. Only the study staff who receive, store, prepare, dispense or

administer the study intervention and are not involved with the safety evaluation will know which study intervention is administered. The unblinded site staff should ensure that the documents on randomization are stored in a secure place where only they have access.

It is to be noted that the unblinded site staff will know whether the injected product is GBP510 or ChAdOx1-S since GBP510 and ChAdOx1-S are different in appearance. The study intervention should be administered in a manner that prevents the participants from identifying the type of study intervention by its appearance.

6.3.3. Code Breaking

The code may be broken in the event of an emergency only when the identification of the study intervention received could influence the medical treatment of the participant. Code-breaking should be limited to the participant(s) experiencing the emergency case.

The blind can be broken by the investigator or a delegate through the IRT system. Once the emergency has been addressed by the site, the investigator or a delegate should make every effort to notify the sponsor prior to code-breaking unless this could delay the treatment of the participant. If a participant's code was broken, the sponsor should be notified within 24 hours after unblinding. The identity of the personnel, date, and reason of code-breaking, and all contact attempts with the sponsor prior to unblinding are to be documented in the source documents.

The IRT manual will provide further details regarding code-breaking procedures.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the qualified unblinded study personnel (i.e., unblinded study vaccinator), under medical supervision. The study vaccinator should confirm the participant has received 0.5mL of either GBP510 mixed with AS03 or ChAdOx1-S in a multi-dose vial. The dose of study intervention and participant identification will be confirmed at the time of dosing by the blinded site staff other than the unblinded vaccinator.

The injection site, date, and time of each dose of study intervention should be recorded in the source documents and eCRF. If a participant fails to receive the study intervention as planned, the reason should also be recorded.

6.5. Dose Modification

Dose modification is not applicable in this study.

6.6. Treatment of Overdose

For this study, any dose of study vaccination greater or earlier than the protocol-specified dose of study vaccine will be considered an overdose.

In case of an overdose, the investigator should:

- Contact the sponsor immediately.
- Closely monitor the participant for any AE/SAEs.
- Record details of the overdose event in the source documents.

6.7. Prior and Concomitant Therapy

Prior and concomitant medications and vaccinations taken from 14 days prior to providing informed consent until the 28-day follow-up visit after completion of vaccination (Visit 7) will be recorded as well as new medications prescribed for new medical conditions / AEs. Any medications that are administered for treatment of SAE, MAAE, or AESI (including pIMDs) may be collected throughout the study period, if necessary.

Name of medication, start and stop dates, dosage, unit, route, frequency, and reason for use will be recorded in the source documents and eCRF. Trade name may be collected for a medication composed of several molecules, and international nonproprietary name (INN) will be preferred for a medication composed of one single molecule.

6.7.1. Prohibited Concomitant Medications

A participant who has received the medications and vaccines within 28 days after the completion of vaccination listed below may be excluded from the per-protocol analysis, and if applicable, the second vaccination may be discontinued in that participant. However, the participant may not be withdrawn from the study, and may be required to return at scheduled visits for immunogenicity and/or safety assessment.

- Receipt of any medications or vaccinations intended to prevent COVID-19 at any time prior to or during study participation.
- Receipt of any vaccine within 4 weeks prior to the 1st study vaccination, through 4 weeks after the last study vaccination (Visit 7), except for influenza vaccination, which may be received at least 2 weeks prior to the 1st study vaccination. This exception includes monovalent pandemic influenza vaccines and multivalent influenza vaccines.
- Receipt of immunoglobulins and/or any blood or blood products within 12 weeks prior to the 1st study vaccination, through 4 weeks after the last study vaccination (Visit 7)
- Chronic use (more than 2 consecutive weeks) of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy; or long-term systemic corticosteroid therapy (≥10mg prednisone/day or equivalent for more than 2 consecutive weeks) within 12 weeks prior to the 1st vaccination, through 4 weeks after the last study vaccination (Visit 7). The use of topical and nasal glucocorticoids will be permitted.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to discontinue study intervention due to AEs including SARS-CoV-2 infection, protocol deviation, or at the request of participant. If study intervention is permanently discontinued, the participant may remain in the study to be evaluated for safety and immunogenicity, if applicable. See "Unscheduled Visit" in Section 1.3 SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed. The reason for discontinuation of study intervention and further study procedures to collect additional information should be documented in the source documents and eCRF.

7.2. Participant Discontinuation/Withdrawal from the Study

Participants have the right to withdraw consent and discontinue from the study at any time, for any reason. A participant may be withdrawn from the study for the following reasons:

- At the discretion of the investigator, IRB/IEC, or sponsor due to safety concerns (i.e., AE/SAEs). The sponsor may consult with the DSMB for withdrawal decision
- At the discretion of the investigator, IRB/IEC, or sponsor due to significant non-compliance with the protocol (i.e., refused follow-up / lost to follow-up, major protocol deviation including newly developed or not pre-identified exclusion criteria are met)
- At request of the participant
- Death
- Pregnancy
- Study termination by sponsor

The reason for a withdrawal should be clearly recorded in the source documents and eCRF.

A participant who discontinues from the study will be encouraged to contact the site staff or return to the trial site for safety follow-ups in accordance with the protocol, and all AEs should be followed through resolution or stabilization. However, if the participant disagrees to be contacted after early termination, the site will not attempt to obtain further safety information and it should be documented in the source documents.

7.3. Lost to Follow-up

A participant will be considered as lost to follow-up if the participant fails to return for scheduled follow-up visits, and is unable to be contacted by the site staff. Reasonable efforts (i.e., telephone calls, certified

mail) should be undertaken to locate or recall them, or at least to determine their health status. At least 3 documented attempts to contact the participant should be documented in the source documents.

8. Study Assessments and Procedures

8.1. Safety Assessments

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

8.1.1. Immediate Post-vaccination Observation

All participants will be kept under observation for at least 30 minutes after each vaccination to ensure their safety. Appropriate medical equipment and emergency medications, including epinephrine (1:1000), should be available on trial site in the event of an anaphylactic, vasovagal, or other immediate allergic reaction. The post-vaccination observation should be documented in the source document. Any AE that occurs during this period will be noted on the source document as follows:

- Unsolicited systemic AEs will be recorded as immediate systemic reactions
- Solicited and unsolicited local reactions and solicited systemic reactions will be recorded in the same way as any other reactions starting on the day of vaccination.
- SAEs will be recorded and reported to the sponsor in the same way as any other SAEs, according to the procedures described in Section 8.1.10.

8.1.2. Solicited Reactions from Day 0 to Day 6 after Each Vaccination

Solicited AEs are pre-defined local and systemic events for which the participant is specifically questioned, and which are noted by the participant in their diary card.

After each vaccination, participants will be provided with a paper participant diary card, an ear thermometer, and a flexible ruler, and will be instructed how to use them to assess the following solicited local and systemic reactions

- Solicited local AEs: redness, swelling, and pain at injection site
- Solicited systemic AEs: fever, nausea/vomiting, diarrhea, headache, fatigue, myalgia, arthralgia, chills

The following items will be recorded by the participants in the participant diary on the day of vaccination and for the next 7 days (Day 0 to 6):

- Daily tympanic temperature
- Daily measurement or maximum severity grade of all other solicited local and systemic reactions
- Action taken for each event (e.g., none, medication, health care provider contact, hospitalized)

If a solicited AE remains beyond 7 days after vaccination, the participant will be asked to report further information including the stop date, and the investigator will record this additional information in the source document and eCRF.

8.1.3. Unsolicited Adverse Events

An unsolicited adverse event is an adverse event that was not solicited using a participant diary. Unsolicited AEs include serious and non-serious AEs, MAAEs, and AESIs (including pIMDs).

Participants will be instructed to record all unsolicited AEs that may occur during 28 days after each vaccination, using the paper diary card.

In the case of SAEs, MAAEs and AESIs, relevant information will be collected and assessed throughout the study, from the 1st study vaccination (Day 0) until 12 months after the last study vaccination (Day 365±14 after Visit 4).

For each unsolicited AE (whether serious or non-serious), the following information is to be recorded by the participant.

- Start and stop dates
- Severity of the event
- Action taken for each event (e.g., none, medication, health care provider contact, hospitalized)

For measurable unsolicited AEs that are part of the list of solicited reactions, the size of the AE as well as the temperature for fever will be collected and analyzed based on the corresponding severity grading scales used for solicited reactions (see Table 5 and 6).

8.1.4. Adverse Event of Special Interest (AESI)

AESI is one of scientific and medical concern specific to the study intervention in this study, and ongoing monitoring and rapid communication by the investigator to the sponsor should be done.

AESIs will be collected with the same level of information as SAE, and reported to the sponsor in accordance with the SAE reporting procedures.

The following AE (but not limited to) will be captured as AESI throughout the study, according to Brighton Collaboration: COVID-19 Adverse Events of Special Interest list.[14]

Table 3. COVID-19 AESI List

AESI included because they are seen with COVID-19 Disease [3,4]
Acute respiratory distress syndrome

Multisystem inflammatory syndrome (children & adults)
Acute cardiovascular injury (includes: myocarditis/pericarditis, microangiopathy, heart failure, stress cardiomyopathy, coronary artery disease arrhythmia)
Coagulation disorder (includes: thrombotic disorders, bleeding disorders)
Anosmia, ageusia
Chilblain – like lesions
Erythema multiforme
Single Organ Cutaneous Vasculitis
Acute kidney injury
Acute liver injury
Acute pancreatitis
Rhabdomyolysis
Subacute thyroiditis
AESI included because they have a proven or theoretical association with immunization in general
Anaphylaxis [1,2]
Thrombocytopenia [1,2,3,4]
Generalized convulsion [1,2]
Acute disseminated encephalomyelitis [4]
Guillain Barré Syndrome [3,4]
AESI included because they have a proven or theoretical association with specific vaccine platform(s)
Acute aseptic arthritis [r-VSV]
Aseptic meningitis [Live vaccines]
Encephalitis / Encephalomyelitis [Live vaccines]
Idiopathic Peripheral Facial Nerve Palsy [Intranasal E.Coli Heat Labile Toxin Adjuvanted Vaccine]
Vaccine associated enhanced disease [1(Formalin inactivated measles/RSV; HIV), 2(Chimeric YF Dengue), 5 (SARS / MERS-CoVs)]
Thrombosis with thrombocytopenia syndrome [Recombinant adenovrial vector vaccines]

[1] *Proven association with immunization encompassing several different vaccines*

[2] *Proven association with vaccine that could theoretically be true for novel COVID-19 vaccines*

[3] *Theoretical concern based on wild type disease immunopathogenesis*

[4] *Theoretical concern related to viral replication during wild type disease*

[5] *Theoretical concern because it has been demonstrated in an animal model with ≥ 1 vaccine platform*

Potential immune-mediated diseases (pIMDs) will also be considered AESIs in this study. pIMDs are a subset of AEs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune etiology. AEs that need to be recorded and reported as pIMDs include those listed in Table 4.
However, the investigator will exercise their medical and scientific judgement in deciding whether

other diseases have an autoimmune origin (that is pathophysiology involving systemic or organ-specific pathogenic autoantibodies) and should also be recorded as a pIMD.
When there is enough evidence to make any of the diagnoses mentioned in Table 4, the AE must be reported as a pIMD. Symptoms, signs or conditions which might (or might not) represent the above diagnoses, should be recorded and reported as AEs but not as pIMDs until the final or definitive diagnosis has been determined, and alternative diagnoses have been eliminated or shown to be less likely.

In order to facilitate the documentation of pIMDs in the eCRF, a pIMD standard questionnaire and a list of preferred terms (PTs) and PT codes corresponding to the below diagnoses will be available to investigators at study start.

Table 4. List of Potential Immune-mediated Diseases

Medical Concept	Additional Notes
Blood disorders and coagulopathies	
Antiphospholipid syndrome	
Autoimmune aplastic anemia	
Autoimmune hemolytic anemia	• Includes warm antibody hemolytic anemia and cold antibody hemolytic anemia
Autoimmune lymphoproliferative syndrome (ALPS)	
Autoimmune neutropenia	
Autoimmune pancytopenia	
Autoimmune thrombocytopenia	• Frequently used related terms include: “autoimmune thrombocytopenic purpura”, “idiopathic thrombocytopenic purpura (ITP)”,“idiopathic immune thrombocytopenia”, “primary immune thrombocytopenia”.
Evans syndrome	
Pernicious anemia	
Thrombosis with thrombocytopenia syndrome (TTS)	
Thrombotic thrombocytopenic purpura	• Also known as “Moschcowitz-syndrome” or “microangiopathic hemolytic anemia”
Cardio-pulmonary inflammatory disorders	

Medical Concept	Additional Notes
Idiopathic Myocarditis/Pericarditis	Including but not limited to: • Autoimmune / Immune-mediated myocarditis • Autoimmune / Immune-mediated pericarditis • Giant cell myocarditis
Idiopathic pulmonary fibrosis	Including but not limited to: • Idiopathic interstitial pneumonia (frequently used related terms include "Interstitial lung disease", "Pulmonary fibrosis", "Immune-mediated pneumonitis") • Pleuroparenchymal fibroelastosis (PPFE)
Pulmonary alveolar proteinosis (PAP)	• Frequently used related terms include: "pulmonary alveolar lipoproteinosis", "phospholipidosis"
Endocrine disorders	
Addison's disease	
Autoimmune / Immune-mediated thyroiditis	Including but not limited to: • Hashimoto thyroiditis (autoimmune hypothyroidism, lymphocytic thyroiditis) • Atrophic thyroiditis • Silent thyroiditis • Thyrotoxicosis
Autoimmune diseases of the testis and ovary	• Includes autoimmune oophoritis, autoimmune ovarian failure and autoimmune orchitis
Autoimmune hyperlipidemia	
Autoimmune hypophysitis	
Diabetes mellitus type I	
Grave's or Basedow's disease	• Includes Marine Lenhart syndrome and Graves' ophthalmopathy, also known as thyroid eye disease (TED) or endocrine ophthalmopathy
Insulin autoimmune syndrome	
Polyglandular autoimmune syndrome	• Includes Polyglandular autoimmune syndrome type I, II and III
Eye disorders	

Medical Concept	Additional Notes
Ocular Autoimmune / Immune-mediated disorders	Including but not limited to: • Acute macular neuroretinopathy (also known as acute macular outer retinopathy) • Autoimmune / Immune-mediated retinopathy • Autoimmune / Immune-mediated uveitis, including idiopathic uveitis and sympathetic ophthalmia • Cogan's syndrome: an oculo-audiovestibular disease • Ocular pemphigoid • Ulcerative keratitis • Vogt-Koyanagi-Harada disease
Gastrointestinal disorders	
Autoimmune / Immune-mediated pancreatitis	
Celiac disease	
Inflammatory Bowel disease	Including but not limited to: • Crohn’s disease • Microscopic colitis • Terminal ileitis • Ulcerative colitis • Ulcerative proctitis
Hepatobiliary disorders	
Autoimmune cholangitis	
Autoimmune hepatitis	
Primary biliary cirrhosis	
Primary sclerosing cholangitis	
Musculoskeletal and connective tissue disorders	
Gout	• Includes gouty arthritis
Idiopathic inflammatory myopathies	Including but not limited to: • Dermatomyositis • Inclusion body myositis • Immune-mediated necrotizing myopathy

Medical Concept	Additional Notes
	• Polymyositis
Mixed connective tissue disorder	
Polymyalgia rheumatica (PMR)	
Psoriatic arthritis (PsA)	
Relapsing polychondritis	
Rheumatoid arthritis	Including but not limited to: • Rheumatoid arthritis associated conditions • Juvenile idiopathic arthritis • Palindromic rheumatism • Still's disease • Felty's syndrome
Sjögren's syndrome	•
Spondyloarthritis	Including but not limited to: • Ankylosing spondylitis • Juvenile spondyloarthritis • Keratoderma blenorrhagica • Psoriatic spondylitis • Reactive Arthritis (Reiter's Syndrome) • Undifferentiated spondyloarthritis
Systemic Lupus Erythematosus	• Includes Lupus associated conditions (e.g. Cutaneous lupus erythematosus, Lupus nephritis, etc.) or complications such as shrinking lung syndrome (SLS)
Systemic Scleroderma (Systemic Sclerosis)	• Includes Reynolds syndrome (RS), systemic sclerosis with diffuse scleroderma and systemic sclerosis with limited scleroderma (also known as CREST syndrome)
Neuroinflammatory/neuromuscular disorders	
Acute disseminated encephalomyelitis (ADEM) and other inflammatory-demyelinating variants	Includes the following: • Acute necrotising myelitis • Bickerstaff's brainstem encephalitis • Disseminated necrotizing leukoencephalopathy (also known as Weston-Hurst syndrome, acute hemorrhagic leuko-

Medical Concept	Additional Notes
	encephalitis, or acute necrotizing hemorrhagic encephalomyelitis) • Myelin oligodendrocyte glycoprotein antibody-associated disease • Neuromyelitis optica (also known as Devic's disease) • Noninfective encephalitis / encephalomyelitis / myelitis • Postimmunization encephalomyelitis
Guillain-Barré syndrome (GBS)	• Includes variants such as Miller Fisher syndrome and the acute motor and sensory axonal neuropathy (AMSAN)
Idiopathic cranial nerve palsies/paresis and inflammations (neuritis)	Including but not limited to: • Cranial nerve neuritis (e.g. Optic neuritis) • Idiopathic nerve palsies/paresis (e.g. Bell's palsy) • Melkersson-Rosenthal syndrome • Multiple cranial nerve palsies/paresis
Multiple Sclerosis (MS)	Includes the following: • Clinically isolated syndrome (CIS) • Malignant MS (the Marburg type of MS) • Primary-progressive MS (PPMS) • Radiologically isolated syndrome (RIS) • Relapsing-remitting MS (RRMS) • Secondary-progressive MS (SPMS) • Uhthoff's phenomenon
Myasthenia gravis	• Includes ocular myasthenia and Lambert-Eaton myasthenic syndrome
Narcolepsy	• Includes narcolepsy with or without presence of unambiguous cataplexy
Peripheral inflammatory demyelinating neuropathies and plexopathies	Including but not limited to: • Acute Brachial Radiculitis (also known as Parsonage-Turner Syndrome or neuralgic amyotrophy) • Antibody-mediated demyelinating neuropathy • Chronic idiopathic axonal polyneuropathy (CIAP) • Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP), including atypical CIDP variants (e.g. multifocal acquired demyelinating sensory and motor neuropathy also known as Lewis-Sumner syndrome)

Medical Concept	Additional Notes
	• Multifocal motor neuropathy (MMN)
Transverse myelitis (TM)	• Includes acute partial transverse myelitis (APTM) and acute complete transverse myelitis (ACTM)
Renal disorders	
Autoimmune / Immune-mediated glomerulonephritis	Including but not limited to: • IgA nephropathy • IgM nephropathy • C1q nephropathy • Fibrillary glomerulonephritis • Glomerulonephritis rapidly progressive • Membranoproliferative glomerulonephritis • Membranous glomerulonephritis • Mesangioproliferative glomerulonephritis • Tubulointerstitial nephritis and uveitis syndrome
Skin and subcutaneous tissue disorders	
Alopecia areata	
Autoimmune / Immune-mediated blistering dermatoses	Including but not limited to: • Bullous Dermatitis • Bullous Pemphigoid • Dermatitis herpetiformis • Epidermolysis bullosa acquisita (EBA) • Linear IgA-mediated bullous dermatosis (LABD), also known as Linear IgA disease • Pemphigus
Erythema multiforme	
Erythema nodosum	
Reactive granulomatous dermatitis	Including but not limited to • Interstitial granulomatous dermatitis • Palisaded neutrophilic granulomatous dermatitis
Lichen planus	• Includes liquen planopilaris
Localised Scleroderma (Morphoea)	• Includes Eosinophilic fasciitis (also called Shulman syndrome)
Psoriasis	
Pyoderma gangrenosum	

Medical Concept	Additional Notes
Stevens-Johnson Syndrome (SJS)	Including but not limited to: • Toxic Epidermal Necrolysis (TEN) • SJS-TEN overlap
Sweet's syndrome	• Includes Acute febrile neutrophilic dermatosis
Vitiligo	
Vasculitis	
Large vessels vasculitis	Including but not limited to: • Arteritic anterior ischemic optic neuropathy (AAION or arteritic AION) • Giant cell arteritis (also called temporal arteritis) • Takayasu's arteritis
Medium sized and/or small vessels vasculitis	Including but not limited to: • Anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified) • Behcet's syndrome • Buerger's disease (thromboangiitis obliterans) • Churg–Strauss syndrome (allergic granulomatous angiitis) • Erythema induratum (also known as nodular vasculitis) • Henoch-Schonlein purpura (also known as IgA vasculitis) • Microscopic polyangiitis • Necrotizing vasculitis • Polyarteritis nodosa • Single organ cutaneous vasculitis, including leukocytoclastic vasculitis, hypersensitivity vasculitis and acute hemorrhagic edema of infancy (AHEI) • Wegener's granulomatosis
Other (including multisystemic)	
Anti-synthetase syndrome	
Capillary leak syndrome	• Frequently used related terms include : "systemic capillary leak syndrome (SCLS)" or "Clarkson's Syndrome"
Goodpasture syndrome	• Frequently used related terms include : "pulmonary renal syndrome" and "anti-Glomerular Basement Membrane disease (anti-GBM disease)"
Immune-mediated enhancement of disease	• Includes vaccine associated enhanced disease (VAED and VAERD). Frequently used related terms include "vaccine-

Medical Concept	Additional Notes
	mediated enhanced disease (VMED)", "enhanced respiratory disease (ERD)", "vaccine-induced enhancement of infection", "disease enhancement", "immune enhancement", and "antibody-dependent enhancement (ADE)
Immunoglobulin G4 related disease	
Langerhans' cell histiocytosis	
Multisystem inflammatory syndromes	Including but not limited to: • Kawasaki's disease • Multisystem inflammatory syndrome in adults (MIS-A) • Multisystem inflammatory syndrome in children (MIS-C)
Overlap syndrome	
Raynaud's phenomenon	
Sarcoidosis	• Includes Loefgren syndrome
Susac's syndrome	

8.1.5. Medically Attended Adverse Events (MAAE)

A MAAE is an AE that leads to hospitalization, and emergency room visit, or otherwise an unscheduled visit to a healthcare professional for any reason. MAAEs will be observed during the study period.

8.1.6. Severity Grading Scales

The severity grading scales used in this study to assess solicited and unsolicited AEs are based on 'Guidance for industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials' by U.S. Food and Drug Administration Center for Biologics Evaluation and Research.[15]

Table 5. Solicited Local AE Grading Scale

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)

Pain	Does not interfere with activity	Repeated use of nonnarcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Redness	2.5-5cm	5.1-10cm	>10cm	Necrosis or exfoliative dermatitis
Swelling	2.5-5cm and does not interfere with activity	5.1-10cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

Table 6. Solicited Systemic AE Grading Scale

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (℃)	38.0-38.4	38.5-38.9	39.0-40	>40
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 IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 – 3 loose stools or < 400 gms/24 hours	4 – 5 stools or 400 – 800 gms/24 hours	6 or more watery stools or > 800gms/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non- narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization

Arthralgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Chills	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization

Table 7. Unsolicited AE Grading Scale

Systemic Illness	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Illness or clinical adverse event	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

8.1.7. Assessment of Causality

The Investigator will assess the causal relationship between unsolicited AE and study intervention administered as either not related or related, based on the following criteria:

- Not related – The AE is clearly / most probably caused by other etiologies such as an underlying condition, therapeutic intervention, or concomitant therapy; or the delay between vaccination and the onset of the AE is incompatible with a causal relationship.
- Related – There is a "reasonable possibility" that the AE was caused by the study intervention administered, meaning that there is evidence or arguments to suggest a causal relationship.

All solicited local and systemic AEs are considered as being related to the study intervention administered, therefore will not require the investigator's medical opinion on relatedness.

Regardless of seriousness and causality, any AEs that persist at the end of the observation period should be followed up by the investigator until their complete resolution or the stabilization of the participant's condition.

8.1.8. Pregnancy testing

Urine or serum hCG pregnancy test will be performed in female participants of childbearing potential before each study vaccination and 6 months after the last study vaccination (Visit 8, Day 168±14 after Visit 4). If a positive pregnancy test result is confirmed, the participant will be withdrawn from further study vaccination but remain in the study for safety and/or immunogenicity monitoring.

8.1.9. Reporting of Pregnancy

If a newly developed or not previously recognized pregnancy is found during the study period, the investigator must report the pregnancy to the sponsor using the pregnancy reporting form, within 24 hours of the investigator's awareness.
Follow-up will be conducted to obtain additional information on the pregnancy and the pregnancy outcome. The investigator will follow the pregnancy until completion or termination of pregnancy. In the case of a live birth, the structural integrity of the neonate should be assessed at the time of birth. Further follow-up of birth outcomes will be determined on a case-by-case basis (e.g., follow-up on preterm infants).
In the event of a termination, the reasons for termination should be specified and, if appliable, a visual inspection of the terminated fetus should be conducted.
Abnormal pregnancy outcomes will be considered SAEs, and the investigator should follow the SAE reporting procedures. Abnormal pregnancy includes, but not limited to: ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, stillbirth, neonatal death, or congenital anomaly.

8.1.10. Reporting of Serious Adverse Events

The investigator must document and report all SAEs occurring during the study period to the sponsor or representatives within 24 hours of the investigator's awareness, regardless of causal relationship. A paper copy of SAE reporting form can be sent to the sponsor via fax, e-mail, or express mail, and EDC system may also be utilized, if available.

For every SAE, the investigator must pursue and obtain adequate information until resolution or stabilization to complete medical assessment of the event for determination of possible causality. Any updated SAE data which is clinically relevant should be reported to the sponsor in a timely manner, preferably within 24 hours of receipt of the information.

The sponsor will submit any reportable SAEs to the relevant health authorities and investigators according to the local regulatory requirements. An investigator who receives SUSAR or other summary or SAEs from the sponsor will notify the IRB/EC according to the local requirements and standard operating procedures.

8.1.11. Physical Examinations

The investigator or designee will perform a full physical examination at screening which may include, but not limited to, the following organs and organ systems: head, eyes, ears, nose, and throat (HEENT), heart, lungs, abdomen, musculoskeletal, extremities, nervous system, and lymph nodes. Height and weight will be measured for BMI calculation at the screening visit only.
A symptom-directed physical examination will be performed at all other timepoints specified in the SoA table (see Section 1.3).

8.1.12. Vital Signs

Vital signs will be measured at time points specified in the SoA (Section 1.3), and include systolic and diastolic blood pressure (after participant is seated for at least 5 minutes), pulse rate, and body temperature.

8.2. COVID-19 Disease Surveillance

If a participant experiences a suspicious symptom of COVID-19, or is notified as having a potential contact with COVID-19 patients, the participant should take examination according to applicable local law and regulations. The participant will be instructed to contact the investigator immediately to notify the fact that the symptoms occurred.

Signs and symptoms of COVID-19 may vary, and in most cases, the participant would experience fever, cough, fatigue, anorexia, shortness of breath, headache, diarrhea, nausea and vomiting. Anosmia or ageusia may precede the onset of respiratory symptoms, and some neurological manifestations including dizziness, agitation, weakness, seizures, or findings suggestive of stroke can occur. Older people may present fatigue, reduced alertness, reduced mobility, diarrhoea, loss of appetite, and confusion.

If the virological (PCR) test result is confirmed as positive, the case will be considered and collected as a confirmed-COVID-19, and the participant will be required to keep contact with the investigator remotely using telephone, and provide (but not limited to) the following information as the COVID-19 illness progresses.

- Onset date of COVID-19 symptoms
- Virologically confirmed and recovery dates of COVID-19
- Clinical care and medications (e.g., oxygen therapy)
- Duration of hospitalization and ICU stay

8.2.1. Participant Diary

Solicited AEs (i.e., reactogenicity) and unsolicited AEs should be monitored and recorded for 7 days and 28 days post each vaccination respectively. Concurrent medications will be routinely collected until 28 days after final administration of study intervention. If there are any ongoing AEs or concurrent medications on the last day of observation period, the stop dates should be obtained from the participant, and entered in the eCRF.

Participants will be required to record any AEs (solicited local and systemic AEs, and unsolicited AEs), SAEs, MAAEs, AESIs (including pIMDs), and concurrent medications during the study period.

8.3. Immunogenicity Assessments

Planned time points for all immunogenicity assessments are provided in the SoA (Section 1.3). Details in regard to sample management (i.e., sample collection, preparation, storage and shipment) can be found in the Laboratory Manual.

8.3.1. Immunogenicity Assessments

Blood samples will be collected for the following assays. ELISA, FRNT, and/or Cellular immunology assay may be performed in a subset of participants and at partial timepoints, and blood samples may be collected in a subset of participants accordingly.

- SARS-CoV-2 RBD-specific IgG ELISA: SARS-CoV-2 IgG ELISA (Enzyme Linked ImmunoSorbent Assay) is the method to quantify the IgG antibody value for the antigen-specific antibody in the pre-vaccination and post-vaccination serum based on indirect ELISA method. It is the principle that the antigen-specific primary antibody or serum containing the antibody is added to the plate to which the specific antigen is bound, and then the enzyme-linked secondary antibody binds to antigen-primary antibody (or serum) complex. At this time, when a substrate such as TMB Substrate is added, HRP linked to the antibody reacts, and the amount of the antibody specific to the target protein can be measured indirectly
- SARS-CoV-2 serum FRNT assay using SARS-CoV-2 wild-type virus: FRNT (Focus Reduction Neutralization Test) is an assay to assess the neutralizing antibody titres in serum induced by viral infection or vaccination using wild-type viruses. FRNT uses immunostaining to visualize “plaques” referred to as foci, and the neutralizing antibodies are assessed by measuring the reduction of foci of viral infection (SARS-CoV-2 wild-type virus) to the susceptibility cell, such as Vero or Vero E6 cell line.
- Cellular immunology assay using ELISpot/FluoroSpot and FACS: ELISpot / FluoroSpot assay quantitatively measures the cytokine secreted in single cells by an antigen-antibody reaction method for the assessment of induced cellular immunity by external antigens- vaccines or infectious pathogens such as viruses and bacteria. Representative cytokines in relation to the Th1 response are IFN-γ, IL-2, TNF-α, and to the Th2 responses is the IL-4. FACS(Fluorescence-activated cell sorting) is a flow cytometry-based assay which detects each T-cell (e.g., CD4+ and CD8+) after inducing cellular immunity with external antigens (e.g.,vaccines or infectious pathogens such as viruses and bacteria).

A summary of the type of samples collected per time point is provided below.

	Visit 1 (screening)	**Visit 2 (pre-1st dose)**	**Visit 4 (pre-2nd dose)**	**Visit 6 (2-week Follow up after Visit 4)**	**Visit 7 (4-week Follow up after Visit 4)**	**Visit 8 (6-month Follow up after Visit 4)**	**Visit 9 (12-month Follow up after Visit 4)**
Immunoassay for detection of SARS-CoV-2 Abs	A few drops of blood			Serum (3.5mL)			
ELISA / Neutralization assay		Serum (10mL)	Serum (10mL)	Serum (10mL)	Serum (10mL)	Serum (10mL)	Serum (10mL)
Cellular immunology assay		Whole blood (32mL)		Whole blood (32mL)		Whole blood (32mL)	Whole blood (32mL)

8.3.2. Biological Samples

All samples will be labeled with codes, so that anonymity of samples will be ensured. The samples may be shared with other researchers as long as confidentiality is maintained.

Any blood samples that remain after the assays outlined in this protocol may be securely stored by SK bioscience or a contracted research laboratory. The sample will be stored for up to 25 years after the end of the study unless a time limitation is required by legal requirements. The samples retained may be used to answer to regulatory questions related to the product's licensure and the potential revalidation of the study results. In addition, participants will be asked to indicate in the ICF whether they will permit the future use of the remaining samples for other exploratory tests. The aim of potential future exploratory research cannot be specified, and may not be related to this particular study. It may be to improve the knowledge of vaccines or infectious diseases, or to improve existing tests or develop new tests to assess vaccines. Human genetic tests will never be performed.

The participant may request to destroy his or her samples at any time. However, any data collected from the samples will still be utilized for this study.

8.4. Study Procedures

8.4.1. Visit 1 – Screening (Day -14 ~ 0)

- Obtain voluntary, written informed consent from the participant. A copy of the signed and dated ICF must be given to the participant, and the details related to informed consent process should be recorded in the source documents.
- Obtain a participant number using the EDC system.
- Obtain demographic data
- Obtain clinically significant medical history within 14 days prior to screening
- Obtain details of prior and concurrent medications and vaccinations taken within 14 days prior to screening.
- Measure vital signs (tympanic temperature, pulse rate, and seated blood pressure)
- Conduct a full physical examination, including, but not limited to, examination of weight, height, the head, eyes, ears, nose, and throat (HEENT), heart, lungs, abdomen, musculoskeletal, extremities, neurological, and lymph nodes
- Perform a qualitative detection of SARS-CoV-2-specific antibodies using a rapid antibody kit
- Perform urine or serum pregnancy test only in a participant of childbearing potential.
- Discuss with the female participant of childbearing potential about maintaining appropriate contraception.
- Ensure all of the inclusion and none of exclusion criteria are met
- Complete the source document and eCRF

8.4.2. Visit 2 – 1st Vaccination (Day 0)

Visit 1(Screening) and Visit 2 (1st Vaccination) will generally be conducted on the same day, if all screening test results are available.

- Obtain clinically significant medical conditions and symptoms that newly occurred since the previous screening visit.
- Obtain details of new medications and vaccinations received since the previous screening visit.
- Measure vital signs (tympanic temperature, pulse rate, and seated blood pressure)
- Conduct a symptom-based physical examination that is focused on changes in health status since the previous visit
- Perform urine or serum pregnancy test only in a participant of childbearing potential.
- Ensure all of the inclusion and none of exclusion criteria are met. Clinically significant respiratory symptoms (e.g., cough, sore throat), febrile illness (>38℃) or acute illness within 72 hours may delay study vaccination, and the participant will be required to return for vaccination 72 hours after the condition has resolved.
- If the participant is eligible, obtain a randomization number and study intervention allocation using the IRT system.
- (Only for Cohort 1 participants) Collect a blood sample (a maximum of 42mL) for immunogenicity assessment. 10mL will be collected to obtain serum samples for ELISA and neutralizing Ab assay, and 32mL will be collected from a subset of approximately 10% of participants priorly selected to harvest PMBC for ELISpot / FluoroSpot and FACS.
- Unblinded study vaccinator will administer 1 dose of study intervention preferably into the deltoid muscle of the non-dominant arm (see the IP Manual). Details of dosing information including the date, site of injection and injection time should be recorded.
- Keep the participant under medical observation for at least 30 minutes after vaccination, and record any acute reactions in the source document.
- Give the participant an ear thermometer for temperature measurements, and a ruler to measure the size of any injection site reactions, and go over the instructions for their use.
- Provide with and explain a 1st paper participant diary
- Discuss with the female participant of childbearing potential about maintaining appropriate contraception.
- Arrange an appointment for the next study visit (Visit 4, Day 28+5 after Visit 2). Remind the participant to expect a telephone call 7 days later (Visit 3, Day 7+3 after Visit 2), and to bring back the 1st participant diary for Visit 4.
- Complete the source document and eCRF.

8.4.3. Visit 3 – 1 week Follow up (Day 7+3 after Visit 2, Telephone Contact)

- Check if the participant experienced any medically attended events (i.e. emergency room visit), hospitalization, or COVID-19 related events since the previous visit

- Check if the participant received any prohibited medications or vaccination since the previous visit
- Remind the participant to continue recording participant diary.
- Remind the female participant of childbearing potential to maintain appropriate contraception.
- Remind the participant to bring back the 1st participant diary for the next visit (Visit 4, Day 28+5 after Visit 2).
- Complete the source document and eCRF.

8.4.4. Visit 4 – 2nd Vaccination (Day 28+5 after Visit 2)

- Retrieve the 1st participant diary, and review the safety data after the 1st vaccination.

  If reactogenicity and safety information is incomplete, interview the participant to obtain additional information. Stop dates and outcomes of any ongoing events should be followed and collected.
- Check new medications and vaccinations, including prohibited ones, received since the previous visit.
- Measure vital signs (tympanic temperature, pulse rate, and seated blood pressure)
- Conduct a symptom-based physical examination that is focused on changes in health status since the previous visit. Check any clinically significant respiratory symptoms (e.g. cough, sore throat), febrile illness (>38℃) or acute illness within 72 hours. If any of them occurred, the participant will be required to return for vaccination 72 hours after the condition has resolved.
- Perform urine or serum pregnancy test only in a female participant of childbearing potential.
- (Only for Cohort 1 participants) Collect a blood sample for immunogenicity assessment. 10mL will be collected to obtain serum samples for ELISA and neutralizing Ab assay.
- Unblinded study vaccinator will administer 1 dose of study intervention preferably into the deltoid muscle of the non-dominant arm (see the IP Manual). Details of dosing information including the date, site of injection, and injection time should be recorded.
- Keep the participant under medical observation for at least 30 minutes after administration, and record any acute reactions in the source document.
- Distribute a 2nd paper participant diary, and remind the participant to continue recording.
- Arrange an appointment for the next study visit (Visit 6, Day 14+3 after Visit 4). Remind the participant to expect a telephone call 7 days later (Visit 5, Day 7+3 after Visit 4), and to bring back the 2nd participant diary for Visit 6.
- Complete the source document and eCRF.

8.4.5. Visit 5 – 1-week Follow up (Day 7+3 after Visit 4, Telephone Contact)

- Check if the participant experienced any medically attended events (e.g., emergency room visit), hospitalization, or COVID-19 related events since the previous visit
- Check if the participant received any prohibited medications or vaccination since the previous visit
- Remind the participant to continue recording participant diary.
- Remind the female participant of childbearing potential to maintain appropriate contraception.
- Remind the participant to bring back the 2nd participant diary for the next study visit (Visit 6, Day

14+3 after Visit 4).

- Complete the source document and eCRF.

8.4.6. Visit 6 – 2-week Follow up (Day 14+3 after Visit 4)

- Review the safety data after the 2nd vaccination based on the 2nd participant diary.

  If reactogenicity information is incomplete, interview the participant to obtain additional information.
- Check new medications and vaccinations, including prohibited ones, received since the previous visit.
- Measure vital signs (body temperature, pulse rate, and seated blood pressure)
- Conduct a symptom-based physical examination that is focused on changes in health status since the previous visit
- Collect a blood sample of 3.5mL for the immunoassay for the in vitro qualitative detection of antibodies of SARS-CoV-2
- (Only for Cohort 1 participants) Collect a blood sample (a maximum of 42mL) for immunogenicity assessment. 10mL will be collected to obtain serum samples for ELISA and neutralizing Ab assay, and 32mL will be collected from a subset of approximately 10% of participants priorly selected to harvest PMBC for ELISpot / FluoroSpot and FACS.
- Remind the participant to contact the site staff if the participant experience any medically attended events (e.g. emergency room visit), hospitalization, or COVID-19 related events
- Remind the participant to continue recording the 2nd participant diary.
- Remind the female participant of childbearing potential to maintain appropriate contraception.
- Arrange an appointment for the next study visit (Visit 7, Day 28+5 after Visit 4), and remind the participant to bring back the 2nd participant diary.
- Complete the source document and eCRF.

8.4.7. Visit 7 – 4-week Follow up (Day 28+5 after Visit 4)

- Retrieve the 2nd participant diary, and review the safety data after the 2nd vaccination.

  If reactogenicity and safety information is incomplete, interview the participant to obtain additional information. Stop dates and outcomes of any ongoing events should be followed and collected.
- Check new medications and vaccinations, including prohibited ones, received since the previous visit.
- Measure vital signs (tympanic temperature, pulse rate, and seated blood pressure)
- Conduct a symptom-based physical examination that is focused on changes in health status since the previous visit
- (Only for Cohort 1 participants) Collect a blood sample for immunogenicity assessment. 10mL will be collected to obtain serum samples for ELISA and neutralizing Ab assay.
- Distribute a 3rd paper participant diary, and remind the participant to continue recording the diary to report MAAEs, SAEs, and COVID-19 related events.
- Remind the participant to contact the site staff if the participant experience any medically attended

events (e.g. emergency room visit), hospitalization, or COVID-19 related events

- Arrange an appointment for the next study visit (Visit 8, Day 168±14 after Visit 4), and remind the participant to bring back the 3rd participant diary.
- Remind the female participant of childbearing potential to use appropriate contraceptive methods until 12 weeks after the last study vaccination.
- Complete the source document and eCRF.

8.4.8. Visit 8 – 6-month Follow up (Day 168±14 after Visit 4)

- Review and record SAEs, MAAEs, AESIs (including pIMDs), or COVID-19 related events occurred since the previous visit based on the 3rd participant diary.

  If safety information is incomplete, interview the participant to obtain additional information. Stop dates and outcomes of any ongoing events should be followed and collected.
- Perform urine or serum pregnancy test only in a female participant of childbearing potential.
- Check any medications that are administered for treatment of SAE, MAAE, or AESI.
- Measure vital signs (tympanic temperature, pulse rate, and seated blood pressure)
- Conduct a symptom-based physical examination that is focused on changes in health status since the previous visit
- (Only for Cohort 1 participants) Collect a blood sample (a maximum of 42mL) for immunogenicity assessment. 10mL will be collected to obtain serum samples for ELISA and neutralizing Ab assay, and 32mL will be collected from a subset of approximately 10% of participants priorly selected to harvest PMBC for ELISpot / FluoroSpot and FACS.
- Remind the participant to contact the site staff if the participant experience any medically attended events (e.g., emergency room visit), hospitalization, or COVID-19 related events
- Arrange an appointment for the next study visit (Visit 9, Day 365±14 after Visit 4), and remind the participant to bring back the 3rd participant diary.
- Complete the source document and eCRF.

8.4.9. Visit 9 – 12-month Follow up (Day 365±14 after Visit 4)

- Retrieve the 3rd participant diary, and review and record SAEs, MAAEs, AESIs (including pIMDs), or COVID-19 related events occurred since the previous visit.

  If safety information is incomplete, interview the participant to obtain additional information. Stop dates and outcomes of any ongoing events should be followed and collected.
- Check any medications that are administered for treatment of SAE, MAAE, or AESI
- Measure vital signs (body temperature, pulse rate, and seated blood pressure)
- Conduct a symptom-based physical examination that is focused on changes in health status since the previous visit
- (Only for Cohort 1 participants) Collect a blood sample (a maximum of 42mL) for immunogenicity assessment. 10mL will be collected to obtain serum samples for ELISA and neutralizing Ab assay, and 32mL will be collected from a subset of approximately 10% of participants priorly selected to harvest

PMBC for ELISpot / FluoroSpot and FACS.

- Complete the source document and eCRF.

8.4.10. Unscheduled Visit

Unscheduled visits may be conducted in the event of a general or severe medical issue such as Grade 3 or 4 local, systemic reaction, SAE, AESI, and/or COVID-19 symptomatology. Participants will be queried regarding AE symptoms and related concomitant medications, and the investigator may perform any medically necessary procedures including but not limited to physical examination and clinical laboratory tests. Unscheduled blood samples may be taken for safety reasons or immunogenicity testing.

Unscheduled visits may be conducted for participants who requested to discontinue from the study for receiving a booster dose of other available COVID-19 vaccine. Long-term immunogenicity and safety assessment may be performed prior to the booster dose of other COVID-19 vaccine via an unscheduled visit, and blood samples may additionally be collected via another unscheduled visit at least two weeks after the booster vaccination with other COVID-19 vaccine for exploratory immunogenicity assessment prior to study termination.

The investigator or designee record will complete the unscheduled visit assessment pages of the source document and eCRF.

9. Statistical Considerations

9.1. Statistical Hypothesis

This study is designed to demonstrate the hypotheses over two co-primary immunogenicity endpoints in seronegative participants assuming the randomization ratio of 2:1 (GBP510 : ChAdOx1-S).

The post-vaccination GMT of neutralizing antibody and the percentages of participants with ≥ 4-fold rise from baseline in neutralization antibody titre will be calculated based on sera collected at 2 weeks after the 2nd study vaccination.

The individual statistical hypothesis is:

- **The ratio of post-vaccination GMTs (GBP510 / ChAdOx1-S)**

  H_0: $\mu_{GBP510}/\mu_{ChAdOx1\text{-}S} \leq 1$ vs H_1: $\mu_{GBP510}/\mu_{ChAdOx1\text{-}S} > 1$

  , where μ is the post-vaccination GMT

- **The difference in the percentages of participants with ≥ 4-fold rise from baseline (GBP510 - ChAdOx1-S)**

  H_0: $P_{GBP510} - P_{ChAdOx1\text{-}S} \leq \delta$ vs H_1: $P_{GBP510} - P_{ChAdOx1\text{-}S} > \delta$

  , where P is the percentages of participants with ≥ 4-fold rise from baseline, and δ is non-inferiority margin (=-5%)

Hypothesis testing will be performed to assess superiority based on the 2-sided 95% CI of the ratio of post-vaccination GMT (GBP510 over ChAdOx1-S), and non-inferiority based on the 2-sided 95% CI of the difference in the percentages of participants with ≥ 4-fold rise from baseline (GBP510 – ChAdOx1-S) in neutralization antibody titre, using 2-sided CIs at 0.05 significance level.

This study is powered to achieve overall 90% power (94.87% power for each endpoint) to demonstrate both superiority and non-inferiority of the co-primary endpoints, and no adjustment for multiple comparisons is required since all endpoints need to be significant to achieve study success.

9.2. Sample Size Determination

9.2.1. Cohort 1 (Immunogenicity Cohort)

Sample size and power for Cohort 1 were estimated based on the results of neutralization assays from the Phase 3 study of ChAdOx1-S[16] and the Phase 1 study of GBP510 (GBP510_002).

Superiority will be shown if a 2-sided 95% CI for the post-vaccination GMT ratio (GBP510 / ChAdOx1-S) has lower limit > 1. The post-2nd vaccination GMT and 95% CI of Control group (ChAdOx1-S) was assumed as 105.373 [88.7, 125.2] based on the result of pseudoneutralization assay from 202 participants, and the standard deviation was estimated as 3.495 using the confidence interval. When the post-vaccination GMT and 95% CI of 1984.01 [1,309.60, 3,005.71] and the standard deviation of 2.31 were assumed for Test group (GBP510) based on the PBNA result in 18 participants, a sample size of 9 (6 in Test group, 3 in Control group) was required to achieve a power of 94.87% for detecting the superiority. However, it was

deemed necessary to take a lot conservative approach in calculating sample size given that each GMT and 95% CI was derived from the different neutralization assays and laboratory locations.

For comparisons of the percentages of participants with ≥ 4-fold rise from baseline, non-inferiority will be shown if a 2-sided 95% CI for the difference between the treatment groups (GBP510 – ChAdOx1-S) has lower limit > -5%. Since the seroconversion rates (≥ 4-fold rise from baseline) of Control and Test group were estimated >99% and 100% respectively in the previous live virus neutralization assays, 99% of participants with ≥ 4-fold rise from baseline was assumed for both Test and Control groups, and a total of 231 participants (154 in Test group, 77 in Control group) was calculated to provide a power of 94.87% for detecting the non-inferiority. However, a more conservative sample size deems to be required for the previously mentioned reason, hence it was determined to recruit approximately 1,950 participants (1,300 in Test group, 650 in Control group)

Consistency Assessment Between Ethinicities

This study is designed as a multi-ethnic study and will be conducted in three ethnicities (Southeast Asia, Caucasian, and Korea). The proportion of participants that is minimally required in Korea was estimated pursuant to Methods developed by PMDA (Pharmaceuticals and Medical Devices Agency) to assess consistency of treatment effect across all ethnicities in multi-ethnic clinical trials. [17][18][19][20][21]

The following assumptions have been considered to estimate the minimum proportion of Korean, and Table 8 presents the unconditional and conditional assurance probability.

- The allocation ratio of participants in the GBP510 and ChAdOx1-S group is 2:1.
- The effect size is same across all ethnicities.
- The proportion of participants in Southeast Asia and Caucasian are 7:1.

1) The ratio of post-vaccination GMTs

The consistency of immunogenicity across all ethnicities will be demonstrated if the ratio of post-vaccination GMTs of neutralizing antibody exceeds 1 in each country, and the assurance probability is greater than 80% as the following formula. [17][18][19]

$$P(\delta_1 > 1 , \delta_2 > 1 , \delta_3 > 1) \geq 0.8$$

where, δ_i = ratio of post-vaccination GMTs (GBP510 / ChAdOx1-S) for the i^{th} ethnicity

i= ethnicity (1 Korean, 2 Southeast Asian, 3 Caucasian)

Unconditional assurance probability

$$P(\hat{\delta}_1 > 1, \hat{\delta}_2 > 1, \hat{\delta}_3 > 1) = \prod_{i=1}^{3} \Phi[\left(z_{1-\frac{\alpha}{2}} + z_{1-\beta}\right)\sqrt{\frac{n_i}{N}}]$$

Conditional assurance probability

$$P\left(\hat{\delta}_1 > 1, \hat{\delta}_2 > 1, \hat{\delta}_3 > 1 \middle| \delta - C > 1\right) where, C = z_{1-\alpha/2}\sqrt{\sum_i f_i\left(\frac{{\sigma_1}^2/k + {\sigma_2}^2}{N}\right)}, f_i = \frac{n_i}{N}$$

$$\frac{P\left(\hat{\delta}_i > 1 \; for \; all \; i \; and \; concluding \; a \; significant \; overall \; treatment \; effect\right)}{1-\beta}$$

$$= \frac{P(z_1 < \sqrt{p_1}C_{\alpha,\beta}, z_2 < \sqrt{p_2}C_{\alpha,\beta}, \cdots, z_i < \sqrt{p_i}C_{\alpha,\beta}, z_{i+1} < z_{1-\beta})}{1-\beta}$$

where, δ= overall treatment effect

σ= standard deviation (σ_1 for Test group, σ_2 for Control group)

k= allocation ratio of Test group/Control group

N= the total number of participants on Control treatment

n_i= the number of participants on each treatment in the i^{th} ethinicity

(z_1, z_2, …, z_i, z_{i+1}) has multivariate normal distribution with variance-covariance matrix

Variance-covariance matrix:

$$\begin{bmatrix} 1 & 0 & \cdots & 0 & \sqrt{p_1} \\ 0 & 1 & & 0 & \sqrt{p_2} \\ \vdots & & \ddots & \vdots & \\ 0 & 0 & \cdots & 1 & \sqrt{p_i} \\ \sqrt{p_1} & \sqrt{p_2} & & \sqrt{p_i} & 1 \end{bmatrix}$$

2) The difference in the percentages of participants with ≥ 4-fold rise from baseline

The consistency of immunogenicity across all ethnicities will be demonstrated if the difference in the percentage of participants with ≥ 4-fold rise from baseline in neutralizing antibody titre exceeds the non-inferiority margin of -5% in each ethnicity, and the assurance probability is greater than 80% as the

following formula. [17][18][19]

$P(\delta_1 > \text{NI margin}, \delta_2 > \text{NI margin}, \delta_3 > \text{NI margin}) \geq 0.8$

where, δ_i = difference in the percentage of participants with ≥ 4-fold rise for the i^{th} ethnicity

i= ethnicity (1 Korean, 2 Southeast Asian, 3 Caucasian)

Unconditional assurance probability

$$P(\hat{\delta}_1 > NI\ margin, \hat{\delta}_2 > NI\ margin, \hat{\delta}_3 > NI\ margin) = \prod_{i=1}^{3} \Phi[\left(z_{1-\frac{\alpha}{2}} + z_{1-\beta}\right)\sqrt{\frac{n_i}{N}}]$$

Conditional assurance probability

$$P\left(\hat{\delta}_1 > NI\ margin, \hat{\delta}_2 > NI\ margin, \hat{\delta}_3 > NI\ margin \middle| \hat{\delta} - C > NI\ margin\right)$$

$$= \frac{P(\hat{\delta}_1 > NI\ margin, \hat{\delta}_2 > NI\ margin, \hat{\delta}_3 > NI\ margin)}{P(\hat{\delta} - C > NI\ margin)}$$

where, $C = z_{1-\alpha/2}\sqrt{\frac{1}{N}\sum_i f_i(p_t(1-p_t)/k + p_c(1-p_c))}$, $f_i = \frac{n_i}{N}$

δ= overall treatment effect

k= allocation ratio of Test group/Control group

N= the total number of participants on Control treatment

n_i= the number of participants on each treatment in the i^{th} ethnicity

p_t= the percentage of participants with ≥ 4-fold rise in GBP510

p_c= the percentage of participants with ≥ 4-fold rise in ChAdOx1-S

Variance-covariance matrix:

$$\begin{pmatrix}\hat{\delta}_1\\ \hat{\delta}_2\\ \hat{\delta}_3\\ \hat{\delta}\end{pmatrix} \sim MVN\left(\begin{pmatrix}p_t-p_c\\ p_t-p_c\\ p_t-p_c\\ \sum_i f_i(p_t-p_c)\end{pmatrix}, \frac{1}{N}\cdot Q\right)$$

, where

$$Q = \begin{pmatrix} \frac{1}{f_1}(p_t(1-p_t)/k + p_c(1-p_c)) & 0 & 0 & p_t(1-p_t)/k + p_c(1-p_c) \\ 0 & \frac{1}{f_2}(p_t(1-p_t)/k + p_c(1-p_c)) & 0 & p_t(1-p_t)/k + p_c(1-p_c) \\ 0 & 0 & \frac{1}{f_3}(p_t(1-p_t)/k + p_c(1-p_c)) & p_t(1-p_t)/k + p_c(1-p_c) \\ p_t(1-p_t)/k + p_c(1-p_c) & p_t(1-p_t)/k + p_c(1-p_c) & p_t(1-p_t)/k + p_c(1-p_c) & \sum\frac{1}{f_i}(p_t(1-p_t)/k + p_c(1-p_c)) \end{pmatrix}$$

Table 8. Unconditional and conditional assurance probability for claiming consistency

Ethnicity			Post-vaccination GMTs		Percentage of participants with ≥ 4-fold rise	
Korean	Southeast Asian	Caucasian	Unconditional	Conditional	Unconditional	Conditional
1%	86.63%	12.38%	57.99%	58.83%	57.46%	64.98%
2%	85.75%	12.25%	62.87%	63.86%	62.23%	71.27%
3%	84.88%	12.13%	66.33%	67.42%	65.63%	75.59%
4%	84.00%	12.00%	69.03%	70.20%	68.28%	78.86%
5%	83.13%	11.88%	71.23%	72.46%	70.45%	81.44%
6%	82.25%	11.75%	73.07%	74.35%	72.26%	83.52%
7%	81.38%	11.63%	74.62%	75.95%	73.81%	85.23%
8%	80.50%	11.50%	75.96%	77.32%	75.14%	86.63%
9%	79.63%	11.38%	77.12%	78.50%	76.29%	87.79%
10%	78.75%	11.25%	78.12%	79.53%	77.29%	88.76%
11%	77.88%	11.13%	79.00%	80.42%	78.17%	89.57%
12%	77.00%	11.00%	79.76%	81.20%	78.93%	90.24%
13%	76.13%	10.88%	80.43%	81.88%	79.61%	90.79%
14%	75.25%	10.75%	81.01%	82.47%	80.20%	91.24%
15%	74.38%	10.63%	81.53%	83.00%	80.72%	91.61%

The estimation indicates that the proportion of Korean participants 5~14% will lead to 80% or greater

assurance probability to demonstrate the consistency between the ethnicites. In practice, inference concerning ethnic results is relevant only if the overall treatment effect is statistically significant.[19] The conditional probability is more relevant than unconditional probability in the confirmatory multi-ethnic trial.[19] In conclusion, this study is planned to enroll at least 11% of Korean participants.

9.2.2. Cohort 2 (Safety Cohort)

The Test group in Cohort 2 will comprise approximately 2,040 participants to collect safety data from at least 3,000 participants vaccinated with 2-dose regimen of GBP510 intended for licensure, combining with the participants from the Test group in Cohort 1 and the earlier clinical trial.

At least 1,700 participants with evaluable safety data are anticipated for the Test group in Cohort 2.

This sample size is based on Food and Drug Administration (FDA) guidance for industry entitled "Development and Licensure of Vaccines to Prevent COVID-19" [22], and may allow to observe at least one adverse event occurring at a frequency of 1 in 1,000. If the true AE rate is 0.1%, with 3,000 participants in a test group, there is 95.03% probability of observing at least 15 AE. Table 9 presents the probabilities of observing at least one particular AE given various true event rates.

Table 9. Probability of Observing at Least One AE for various event rates.

True Event Rate	n=1,700	n=2,040	n=3,000
0.1%	81.75	87.01	95.03
0.5%	99.98	>99.99	>99.99
1.0%	>99.99	>99.99	>99.99
2.0%	>99.99	>99.99	>99.99
3.0%	>99.99	>99.99	>99.99
4.0%	>99.99	>99.99	>99.99
5.0%	>99.99	>99.99	>99.99
7.0%	>99.99	>99.99	>99.99
10.0%	>99.99	>99.99	>99.99

9.3. Analysis Sets

For analysis purposes, the following populations are defined:

Population	Description
ITT	All participants who are randomized

Safety set (SS)	All participants who receive at least 1 dose of study intervention. Participants will be analyzed according to the study intervention they actually received.
Full analysis set (FAS)	All participants who received at least 1 dose of the study vaccine and have a valid both pre- and at least one post-vaccination immunogenicity assessment results. For immunogenicity analyses, participants will be analyzed by the study intervention to which they were randomized.
Per-protocol set (PPS)	All participants who complete the vaccination schedule in an uninfected state with SARS-CoV-2 and have no major protocol deviations. A participant will be confirmed to be uninfected if the baseline neutralizing antibody titre is below LLOQ in wild-type virus neutralization assay, and no history of SARS-CoV-2 infection is confirmed by medical interview within the predefined period for PPS1 or PPS2 (A negative result in the qualitative detection of antibodies to SARS-CoV-2 at Visit 6 will additionally be required for PPS1). Two PPS will be defined as below: ▪ PPS1 for Primary stage (Visit 1 to 6) ▪ PPS2 for Extension stage (Visit 7 to 9) Participants will be excluded from the PPS1 if they present with, but not limited to, at least one of the following major protocol deviations, or any of their blood samples collected until Visit 6 (Day 14+3 after Visit 4) did not produce valid test results. ▪ Participant did not meet all inclusion criteria or met at least one of the exclusion criteria ▪ Participant did not complete the vaccination schedule ▪ Preparation and / or administration of study intervention was not done as per-protocol ▪ Participant did not receive the study intervention in the proper time window ▪ Any of the blood samples were not drawn, or not drawn in the proper time window until Visit 6 (Day 14+3 after Visit 4) ▪ Participant received a protocol-prohibited medication or vaccine from Visit 2 (Day 0) to Visit 6 (Day 14+3 after Visit 4) (see Section 6.7.1)

	In addition to the reasons listed above, participants will also be excluded from the PPS2 if any of their additional blood samples from Visit 7 (Day 28+5 after Visit 4) to Visit 9 (Day 365±14 after Visit 4) were not drawn, or not drawn in the proper time window.

9.4. Statistical Analyses

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

9.4.1. General Consideration

Summary statistics for continuous variables will include number of observations (n), mean, standard deviation, minimum, median, and maximum. Discrete (Categorical) variables will be summarized by frequency counts and percentage (n and %) or contingency tables.

Missing data will not be imputed for both safety and immunogenicity assessment. However, missing causality will be considered as related at the time of statistical analysis.

9.4.2. Primary Endpoints (Immunogenicity)

The interim analysis will be performed for both the PPS1 and FAS, but the conclusion will be made from PPS1 results.

Statistical methodology will be based on the 2-sided 95% CI of the ratio of post-vaccination GMTs (GBP510 / ChAdOx1-S) and the difference in percentages of participants with ≥ 4-fold rise from baseline (GBP510 – ChAdOx1-S) in neutralization antibody titre between Test group (GBP510) and Control group (ChAdOx1-S). The post-vaccination GMTs and the percentages of participants with ≥ 4-fold rise from baseline will be calculated based on sera collected at 2 weeks after the 2nd study vaccination (Visit 6).

Adjusted estimates of GMTs, and their associated 95% CIs will be determined using analysis of covariance (ANCOVA) model with treatment group, age group (18~64, ≥65) as factors, and baseline antibody level as covariate. The 95% CI of percentage of participants ≥ 4-fold rises will be calculated based on Clopper-Pearson method.

Superiority will be achieved if the lower limit of the 2-sided 95% CI for the ratio of post-vaccination GMTs exceeds 1, and non-inferiority will be demonstrated if the lower limit of the 2-sided 95% CI for the difference of the percentage of participants with ≥ 4-fold rise exceeds a non-inferiority margin of -5%.

9.4.3. Secondary Endpoints (Immunogenicity)

The analysis of secondary immunogenicity endpoints will be performed on the PPS1, PPS2, and FAS.

The point estimates and their 95% CI of the following parameters will be presented for each treatment group. The 95% CI will be calculated based on the t-distribution of the log-transformed values for

geometric means or geometric mean fold rises, then back transformed to the original scale for presentation. The 95% CI of percentage of participants ≥ 4-fold rises will be calculated based on Clopper-Pearson method.

- GMT of SARS-CoV-2 RBD-binding IgG antibody measured by ELISA at the following time points: before and 4 weeks after 1st vaccination, 2 weeks, 4 weeks, 6 months, and 12 months after 2nd vaccination
- GMFR of SARS-CoV-2 RBD-binding IgG antibody measured by ELISA from baseline to the following time points: 4 weeks after 1st vaccination, 2 weeks, 4 weeks, 6 months, and 12 months after 2nd vaccination
- Percentage of participants with ≥ 4-fold rise in ELISA SARS-CoV-2 RBD-binding IgG titre from baseline (Visit 2) to the following time points: 4 weeks after 1st vaccination, 2 weeks, 4 weeks, 6 months, and 12 months after 2nd vaccination
- GMT of neutralizing antibody to the SARS-CoV-2 measured by wild-type virus neutralization assays at the following time points: before and 4 weeks after 1st vaccination, 2 weeks, 4 weeks, 6 months, and 12 months after 2nd vaccination
- GMFR of neutralizing antibody to the SARS-CoV-2 measured by wild-type virus neutralization assays from baseline to the following time points: 4 weeks after 1st vaccination, 2 weeks, 4 weeks, 6 months, and 12 months after 2nd vaccination
- Percentage of participants with ≥ 4-fold rise in wild-type virus neutralizing antibody titre from baseline (Visit 2) to the following time points: 4 weeks after 1st vaccination, 2 weeks, 4 weeks, 6 months, and 12 months after 2nd vaccination
- Cell-mediated response for both Th1 and Th2 cytokines (e.g., INF-γ, TNF-α, IL-2, and IL-4 produced by T lymphocytes) measured by ELISpot / FluoroSpot, and for both CD4+ and CD8+ T-cells measured by FACS in a subset of 10% participants in Cohort 1 at the following time points: before 1st vaccination, 2 weeks, 6 months, and 12 months after 2nd vaccination

Subgroup analyses will be performed to assess the consistency of immunogenicity across subgroups including but may not be limited to: age strata (18-64 or ≥ 65 years). More details of further subgroup analyses and potential covariate-adjusted analyses will be described in the Statistical Analysis Plan (SAP).

9.4.4. Secondary Endpoints (Safety)

Safety endpoints will be analyzed for participants in the safety set (SS) who received at least 1 dose of study intervention.

Numbers and percentages (with 95% CIs based on the Clopper-Pearson method) of participants with at least one event of the following endpoints will be presented by treatment group.

- Immediate systemic reactions within 30 minutes post each vaccination
- Solicited local and systemic AEs during 7 days (Day 0-6) post each vaccination, summarized by seriousness, duration, action taken, and the maximum severity over 7 days after each vaccination.
- Unsolicited AEs during 28 days post each vaccination coded by preferred term (PT) and system organ class (SOC) using the latest version of MedDRA. Unsolicited AE will be summarized by causality, seriousness, action taken, and severity.
- SAEs, MAAEs, AEs leading to study withdrawal, and AESIs (including pIMDs) throughout the study period will be summarized in each MedDRA PT and SOC, by causality, seriousness criteria, action taken, and severity. Detailed event description will also be presented.

9.4.5. Exploratory Endpoints

- To describe the immune responses induced in adults aged 18 years and older who proved to be seropositive prior to study vaccination and/or proved to be infected during the study

  Immune responses in seropositive participants who have been enrolled due to false negative results of SARS-CoV-2 antibody test at screening (Visit 1), or in participants who were identified to had been infected during the study period by the positive results of in vitro immunoassays for detection of SARS-CoV-2 antibodies at Visit 6 will be summarized and compared between treatment groups, if applicable.

- To describe the immune responses against circulating strains, including the variants of concern

  Immune response in terms of IgG and/or neutralizing antibody against the variant strains of specific interest will be summarized by treatment group, and compared to the immune response against the parent strain.

- To compare the incidence rates of virologically-confirmed COVID-19 between Test group and Control group

  The incidence rates and severities to be estimated based on any symptomatic SARS-CoV-2 infection diagnosed ≥ 14 days after completion of the 1st or 2nd study vaccination. The severity of COVID-19 cases will be categorized using the WHO severity definitions based on clinical indicators. Clinically relevant disease severity should be evaluated using the current WHO COVID-19 disease severity categorization in WHO living guidance entitled “COVID-19 Clinical management”.[23] If applicable, virus genome sequencing may to performed to identify a strain of SARS-CoV-2 for the COVID-19 cases during the study period.

WHO Severity definitions	
Critical COVID-19:	Defined by the criteria for acute respiratory distress syndrome (ARDS), sepsis, septic shock, or other conditions that would normally require the provision of life-sustaining therapies such

	as mechanical ventilation (invasive or non-invasive) or vasopressor therapy.
Severe COVID-19:	Defined by any of: ▪ Oxygen saturation < 90% on room air. ▪ Respiratory rate > 30 breaths/min ▪ Signs of severe respiratory distress (accessory muscle use, inability to complete full sentences)
Non-severe COVID-19:	Defined as absence of any criteria for severe or critical COVID-19.

* *Caution*: The panel noted that the oxygen saturation threshold of 90% to define severe COVID-19 was arbitrary and should be interpreted cautiously. For example, clinicians must use their judgment to determine whether a low oxygen saturation is a sign of severity or is normal for a given patient with chronic lung disease. Similarly, a saturation > 90–94% on room air is abnormal (in patient with normal lungs) and can be an early sign of severe disease, if patient is on a downward trend. Generally, if there is any doubt, the panel suggested erring on the side of considering the illness as severe

- To describe the consistency of immunogenicity across ethnicities
  Based on Method 2 assumption of PMDA which was used to calculate the proportions of participants for each ethnicity, the ratio of post-vaccination GMTs (GBP510 / ChAdOx1-S) of neutralizing antibody will be compared with 1, and the difference in the percentages of participants with ≥ 4-fold rise from baseline (GBP510 – ChAdOx1-S) in neutralization antibody titre will be compared with -5%. If the point estimate values of both the post-vaccination GMT ratio and the difference in the percentages of participants with ≥ 4-fold rise exceed 1 and -5% respectively in each ethnicity, it can be concluded that the consistency between ethnicities has been demonstrated.

- To conduct various exploratory studies on samples collected from study participants to further evaluate the safety and/or immunogenicity profile of GBP510 vaccines

9.4.6. Other Analyse(s)

Any further analyses will be described in the SAP.

9.5. Interim and Final Analyses

The interim analysis will be performed on demographics, safety, and immunogenicity data obtained from participants up to Visit 7 (Day 28+5 after Visit 4). However, the immunogenicity assessment may only be conducted based on sera collected at baseline and 2 weeks post 2nd vaccination for the interim analysis,

and the other sera obtained up to Visit 7 may subsequently be analyzed after database lock for the interim analysis, and the result may be reflected in the interim or final clinical study report (CSR).

The final analysis will be further conducted on safety and immunogenicity data obtained up to Visit 9 (Day 365±14 after Visit 4) after the 2nd database lock.

The blind will be broken for these analyses, but the randomization schedule will not be provided to investigators and other blinded study staff, and the laboratory personnel performing the immunogenicity tests. They will remain blind to treatment group assigned until final database lock after Visit 9 (Day 365±14 after Visit 4).

10. Supporting Documentation and Operational Considerations

10.1. Appendix: 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
- ICH Good Clinical Practice (GCP) E6(R2) Guidelines
- Applicable local laws and regulations

The protocol, protocol amendments, ICF, Investigator 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 NRA approval prior to initiation.

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 applicable local laws and regulations, ICH guidelines, the IRB/IEC.

The sponsor will have an insurance policy to cover any liabilities that may arise from use of study intervention and / or the study protocol.

10.1.2. Financial Disclosure

The investigator may be required to provide financial disclosure information to allow the sponsor to provide disclosure statements required by local requirements.

10.1.3. Informed Consent Process

Informed consent must be obtained before any study procedures are performed.

The investigator or authorized designee will explain the nature of the study including the purpose of the study, the procedures and potential risks associated with participation to the participant or

their legally authorized representative, and answer all questions regarding the study. The participant must have sufficient time and opportunity to ask any questions.

Participants must be informed that their participation is voluntary. Once the investigator is assured that the participant understands the implications of participating in the study, participants will be required to sign a statement of informed consent that meets the requirements of local regulations, ICH guidelines, where applicable, and the IRB/IEC. The authorized person obtaining the informed consent must also sign the ICF, and a copy of the ICF(s) must be provided to the participant or their legally authorized representative.

The source document 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.

If new information becomes available that may be relevant to the participant's willingness to continue participation in the study, this will be provided to the participant in a timely manner. Participants must be re-consented to the most current version of the ICF(s) with substantial amendments during their participation in the study.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate agreement checkbox will be marked to document a participant's agreement to allow any remaining specimens to be used for exploratory research.

10.1.4. Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred. All records will be kept in a secured storage area with limited access.

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

An independent DSMB will be organized, and periodically review accumulating blinded and unblinded safety data. Participant safety will also be continuously monitored by the DSMB, which includes safety signal detection at any time during the study. The DSMB will recommend whether to stop or continue

enrollment and study vaccination according to their medical judgement, and may suggest amending study design.

See the DSMB charter for further details including regular and specific time points for meetings.

All safety data summarized will be reviewed by the DSMB in an unblinded manner to facilitate possible decisions of study discontinuation. The safety reports will be summarized based on preliminary data that have not been subject to verification and database lock, and provided by an independent statistician who won't be communicated to the sponsor.

Safety data will also be reviewed by the sponsor in a blinded manner, and in particularly, for identification of the following events that could jeopardize the safety of the participants, thus potentially contribute to a requirement to pause the study vaccination.

Halting Rules
▪ Any death assessed as related to the study vaccine ▪ Any safety signal identified as significant concern by the DSMB or the sponsor following the review of the safety data including but not limited to: SAEs, SUSARs, AESIs, MAAEs, solicited and unsolicited AEs ▪ Any unfavorable imbalance identified by the DSMB between Test Vaccine and Control Vaccine for severe or serious medical conditions, including COVID-19 cases or severity of COVID-19 symptoms (e.g. VAED)

If any one of the above halting rules is met, enrollment and study vaccination is paused, and the sponsor and DSMB will review the case to make a recommendation as to whether enrollment and study vaccination should be allowed to resume. Case unblinding for the sponsor may be performed for above reviews if necessary.

Formal recommendation provided by DSMB to the sponsor regarding the continuation or discontinuation of the study may be forwarded by the investigator to the IRB/IEC, or by the sponsor to the relevant regulatory authorities according to local laws and regulations.

10.1.6. Dissemination of Clinical Study Data

SK bioscience will publicly disclose clinical study results by posting the results on www.clinicaltrials.gov and/or other public registries in accordance with applicable local laws and regulations.

10.1.7. Data Quality Assurance

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents. A quality assurance audit may be performed at any time by the sponsor's clinical quality management department or by independent

auditors to verify that the study has been conducted according to the protocol, relevant SOPs, GCP, ICH requirements, and other applicable regulations. The Investigator or designee must be available for these visits, and must allow the direct access to participant medical files and CRF.

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee 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.

Monitoring details describing strategy (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 designee 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 and sponsor at least for 3 years after the product marketing authorization or study completion whichever comes later, 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. What constitutes source data should be defined, and source documents are filed at the investigator's site.

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

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. The investigator or designee must be available to answer any queries forwarded by the study monitors or other study staff, and all data-related queries must be completed prior to database lock.
- The safety and rights of participants are being protected.
- The study is being conducted in accordance with the currently approved protocol and any other

study agreements, any study-specific guidelines, all applicable regulatory requirements including GCP, and relevant SOPs. Any identified problems including protocol deviations will be discussed with the investigator, and CAPA will be determined, as appropriate.

10.1.9. Study and Site Start and Closure

[First Act of Recruitment]

The first participant's first visit (FSFV) will be considered the first act of recruitment, and will be the study start date.

[Study/Site Termination]

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor (e.g., discontinuation of further study intervention development). 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:

- Repeated significant failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines,
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator,
- Total number of participants included earlier than expected.

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

10.1.10. Publication Policy

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

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

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. If there is any conflict between the contract and this protocol, the contract will prevail as to publication rights.

10.2. Appendix: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.2.1. Definition of AE

AE/ADR 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. ▪ ADRs are all noxious and unintended responses to study intervention related to any dose of study intervention. NOTE: The phrase "responses to study intervention" means that a causal relationship between the study intervention and adverse event is at least a reasonable possibility (i.e., the relationship cannot be ruled out).

Events Meeting the AE Definition
▪ Any abnormal laboratory test results (e.g., hematology, clinical chemistry) or other safety assessments (e.g. ECG, 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 conditions detected or diagnosed after study vaccination even though it may have been present before the start of the study. ▪ Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

Events <u>NOT</u> Meeting the AE Definition
▪ Any clinically significant abnormal laboratory findings or other abnormal safety assessments which 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.

10.2.2. Definition of SAE

An SAE is defined as any serious adverse event that, at any dose:

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other medically important conditions

Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the health of the participant or may require intervention to prevent one of the other outcomes listed in the above definition. These important medical events should also usually be considered serious. (examples of such events are intensive treatment in an emergency room or at home for allergic

bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse).

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

AE and SAE Recording

- When an AE/SAE occurs, investigator should review all documentation (e.g., hospital medical records, laboratory reports, and diagnostics reports, prescription) 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 in lieu of completion of the paper or eCRF SAE report form.
- There may be instances when copies of medical records for certain cases are requested by the sponsor. 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.
- 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.

Assessment of Causality

- The investigator and sponsor are obligated respectively to assess the relationship between study intervention and each occurrence of each AE/SAE.
- The causality by the investigator should not be downgraded by the sponsor.
- If the sponsor doesn't agree with the investigator's assessment, both assessment of investigator and sponsor should be included in the final report.
- And the worse assessment between the two assessments should be considered as the final causality assessment. A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study vaccination will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) 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.

- 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. 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.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

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 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.
- If a participant dies during participation in the study or during a recognized follow-up period, when available the investigator will provide the sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information may be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data which is clinically significant to the sponsor in a timely manner, preferably within 24 hours of receipt of the information.

10.2.4. Reporting of SAEs

SAE Reporting to the sponsor

- The primary mechanism for reporting an SAE to the sponsor will be the paper SAE data collection tool.
- The site may also use the electronic SAE data collection tool, if applicable.

10.3. Appendix: Contraceptive and Barrier Guidance

Female participants of childbearing potential must use one of the following contraceptive methods which is considered appropriate given local availability and regulations. Female participants who are surgically sterile or postmenopausal with amenorrhea for at least 12 months are not subject for pregnancy test

- Vasectomized male partner (only if the partner is the sole sexual partner of the female participant of childbearing potential)
- Sexual abstinence : 100% of no sexual intercourse
- Condom (with or without spermicide) use by female participants of childbearing potential or their male partner, combined with use of either cervical cap or diaphragm with spermicide (double barrier methods)
- Hormone contraception associated with inhibition of ovulation (e.g., oral, intravaginal, implantable, transdermal, injectable)
- Intra-uterine device

10.4. Appendix: Abbreviations

Ab	Antibody
AE	Adverse Events
AESI	Adverse Events of special interest
ADR	Adverse Drug Reactions
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCA	Anti Neutrophil Cytoplasmic Antibody
ARDS	Acute Respiratory Distress Syndrome
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CAPA	Corrective Action and Preventive Action
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CMI	Cell Medicated Immunity
CONSORT	Consolidated Standards of Reporting Trials
CoP	Correlates of Protection
COVID	Corona Virus Disease
CREST	Calcinosis, Raynaud phenomenon, Esophageal dysmotility, Sclerodactyly, and Telangiectasia
CPE	Cytopathic Effect
CRF	Case Report Form
DNA	Deoxyribo Nucleic Acid
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
e-diary	Electronic Diary

ELISA	Enzyme-linked Immunosorbent Assay
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSFV	First Participant's First Visit
GCP	Good Clinical Practice
GMT	Geometric Mean Titre
GMFR	Geometric Mean Fold Rise
hCG	Human Chorionic Gonadotropin
HEENT	Head Eyes Ears Nose and Throat
HIV	Human Immunodeficiency Virus
HRP	Horseradish peroxidase
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization
ICS	Intracellular Cytokine Staining
ICU	Intensive Care Unit
IEC	Independent Ethics Committees
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IL	Interleukin
IM	Intramuscular
INF	Interferon
INN	International Nonproprietary Name
IMP	Investigational Medicinal Product
IPD	Institute for Protein Design
IRB	Institutional Review Boards
IRT	Interactive Response Technology
ITT	Intention to Treat

MAAE	Medically Attended Adverse Events
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East Respiratory Syndrome
MFDS	Ministry of Food and Drug Safety
mRNA	Messenger Ribo Nucleic Acid
n	Number
NA	Not applicable
NAb	Neutralizing Antibody
NIMP	Non Investigational Medicinal Product
NRA	National Regulatory Authority
LMIC	Low Middle Income Countries
PBMC	Peripheral blood mononuclear cell
PBNA	Pseudovirion-based Neutralisation Assay
pIMD	Potential immune-mediated diseases
PPS	Per Protocol Set
PT	Preferred Term
RBD	Receptor-binding Domain
RBC	Red Blood Cell Count
RSV	Respiratory Syncytial Virus
SAE	Serious adverse events
SAP	Statistical analysis plan
SARS-CoV	Severe Acute Respiratory Syndrome Coronavirus
SoA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
SR	Serum
SS	Safety Set
SUSAR	Suspected Unexpected Serious Adverse Reaction

TMB	Tetramethylbenzidine
UW	University of Washington
VAED	Vaccine-associated Enhanced Disease
WB	Whole Blood
WBC	Whole Blood Cell Count
WHO	World Health Organization
wtVNA	wild-type Virus Neutralization Assay

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