# Supplementary appendix

Supplement to: Song JY, Choi WS, Heo JY, et al. Safety and immunogenicity of a SARS-CoV-2 recombinant protein nanoparticle vaccine (GBP510) adjuvanted with AS03: a phase 1/2, randomised, placebo-controlled, observer-blinded trial.

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# I. Supplementary Tables and Figures

**Table S1.** Adverse event of special interest (AESI) relevant to coronavirus disease 2019 (COVID-19)

| Body System | AESI relevant to COVID-19 |
|---|---|
| Immunologic | Enhanced disease following immunization<br>Anaphylaxis<br>Vasculitis |
| Respiratory | Acute Respiratory Distress Syndrome (ARDS) |
| Cardiac | Acute cardiac injury including:<br>▪ Microangiopathy<br>▪ Heart failure and cardiogenic shock<br>▪ Stress cardiomyopathy<br>▪ Coronary artery disease<br>▪ Arrhythmia<br>▪ Myocarditis, pericarditis |
| Hematologic | Coagulation disorder:<br>▪ Deep vein thrombosis<br>▪ Pulmonary embolus<br>▪ Cerebrovascular stroke<br>▪ Limb ischemia<br>▪ Hemorrhagic disease<br>▪ Thrombocytopenia |
| Renal | Acute kidney injury |
| Gastrointestinal | Liver injury |
| Neurologic | Guillain Barré Syndrome<br>Generalized convulsion<br>Anosmia, ageusia<br>Meningoencephalitis<br>Acute disseminated encephalomyelitis |
| Dermatologic | Chilblain-like lesions<br>Single organ cutaneous vasculitis<br>Erythema multiforme |

**Table S2.** List of potential immune-mediated diseases [6]

| Neuroinflammatory disorders | Musculoskeletal disorders | Skin disorders |
|---|---|---|
| ▪ Cranial nerve neuropathy, including paralysis and paresis (eg, Bell's palsy).<br>▪ Optic neuritis.<br>▪ Multiple sclerosis.<br>▪ Transverse myelitis.<br>▪ Guillain-Barré syndrome, including Miller Fisher syndrome and other variants.<br>▪ Acute disseminated encephalomyelitis, including site specific variants, eg, noninfectious encephalitis, encephalomyelitis, myelitis, myeloradiculoneuritis.<br>▪ Myasthenia gravis, including Lambert-Eaton myasthenic syndrome.<br>▪ Demyelinating peripheral neuropathies including:<br>- Chronic inflammatory demyelinating polyneuropathy.<br>- Multifocal motor neuropathy.<br>- Polyneuropathies associated with monoclonal gammopathy.<br>▪ Narcolepsy. | ▪ Systemic lupus erythematosus and associated conditions.<br>▪ Systemic scleroderma (systemic sclerosis), including:<br>- Diffuse scleroderma.<br>- CREST syndrome.<br>▪ Idiopathic inflammatory myopathies, including:<br>- Dermatomyositis.<br>- Polymyositis.<br>▪ Anti-synthetase syndrome.<br>▪ Rheumatoid arthritis and associated conditions including:<br>- Juvenile idiopathic arthritis.<br>- Still's disease.<br>▪ Polymyalgia rheumatica.<br>▪ Spondyloarthropathies, including:<br>- Ankylosing spondylitis.<br>- Reactive arthritis (Reiter's syndrome).<br>- Undifferentiated spondyloarthritis.<br>- Psoriatic arthritis.<br>- Enteropathic arthritis.<br>▪ Relapsing polychondritis.<br>▪ Mixed connective tissue disorder.<br>▪ Gout. | ▪ Psoriasis.<br>▪ Vitiligo.<br>▪ Erythema nodosum.<br>▪ Autoimmune bullous skin diseases (including pemphigus, pemphigoid, and dermatitis herpetiformis).<br>▪ Lichen planus.<br>▪ Sweet's syndrome.<br>▪ Localized scleroderma (morphea). |
| **Vasculitis** | **Blood disorders** | **Others** |
| ▪ Large vessels vasculitis including:<br>- Giant cell arteritis | ▪ Autoimmune hemolytic anemia.<br>▪ Autoimmune | ▪ Autoimmune glomerulonephritis including: |

| | | |
|---|---|---|
| (temporal arteritis).<br>- Takayasu's arteritis.<br>▪ Medium sized and/or small vessels vasculitis including:<br>- Polyarteritis nodosa.<br>- Kawasaki's disease.<br>- Microscopic polyangiitis.<br>- Wegener's granulomatosis (granulomatosis with polyangiitis).<br>- Churg–Strauss syndrome (allergic granulomatous angiitis or eosinophilic granulomatosis with polyangiitis).<br>- Buerger's disease (thromboangiitis obliterans).<br>- Necrotizing vasculitis (cutaneous or systemic).<br>- Anti-Neutrophil Cytoplasmic Antibody (ANCA) positive vasculitis (type unspecified).<br>- Henoch-Schonlein purpura (IgA vasculitis).<br>- Behcet's syndrome.<br>- Leukocytoclastic vasculitis. | thrombocytopenia.<br>▪ Antiphospholipid syndrome.<br>▪ Pernicious anemia.<br>▪ Autoimmune aplastic anemia.<br>▪ Autoimmune neutropenia.<br>▪ Autoimmune pancytopenia. | - IgA nephropathy.<br>- Glomerulonephritis rapidly progressive.<br>- Membranous glomerulonephritis.<br>- Membranoproliferative glomerulonephritis.<br>- Mesangioproliferative glomerulonephritis.<br>- Tubulointerstitial nephritis and uveitis syndrome.<br>▪ Ocular autoimmune diseases including:<br>- Autoimmune uveitis.<br>- Autoimmune retinitis.<br>▪ Autoimmune myocarditis.<br>▪ Sarcoidosis.<br>▪ Stevens-Johnson syndrome.<br>▪ Sjögren's syndrome.<br>▪ Alopecia areata.<br>▪ Idiopathic pulmonary fibrosis.<br>▪ Goodpasture syndrome.<br>▪ Raynaud's phenomenon. |
| Liver disorders | Gastrointestinal disorders | Endocrine disorders |
| ▪ Autoimmune hepatitis.<br>▪ Primary biliary cirrhosis.<br>▪ Primary sclerosing cholangitis. | ▪ Inflammatory bowel disease, including:<br>- Crohn's disease.<br>- Ulcerative colitis.<br>- Microscopic | ▪ Autoimmune thyroiditis (Hashimoto thyroiditis).<br>▪ Grave's or Basedow's disease.<br>▪ Diabetes mellitus type 1. |

| | | |
|---|---|---|
| ▪ Autoimmune cholangitis. | colitis.<br>- Ulcerative proctitis.<br>▪ Celiac disease.<br>▪ Autoimmune pancreatitis. | ▪ Addison's disease.<br>▪ Polyglandular autoimmune syndrome.<br>▪ Autoimmune hypophysitis. |

**Table S3. Solicited local adverse events - number of participants experiencing the events (safety set)**

| | 10µg GBP510 with AS03 (N = 101) | 10µg GBP510 (N = 10) | 25µg GBP510 with AS03 (N = 104) | 25µg GBP510 (N = 51) | Placebo (N = 61) |
|---|---|---|---|---|---|
| Adverse Events after any vaccine injection, n (%), | | | | | |
| Injection Site Pain | 89 (88·12) | 5 (50·00) | 96 (92·31) | 34 (66·67) | 13 (21·31) |
| Injection Site Redness | 8 (7·92) | 0 (0·00) | 11 (10·58) | 0 (0·00) | 0 (0·00) |
| Injection Site Swelling | 11 (10·89) | 0 (0·00) | 14 (13·46) | 2 (3·92) | 0 (0·00) |
| Adverse Events after the 1st vaccination, n (%) | | | | | |
| Injection site pain | 83 (82·18) | 2 (20·00) | 89 (85·58) | 25 (49·02) | 8 (13·11) |
| Injection site redness | 2 (1·98) | 0 (0·00) | 3 (2·88) | 0 (0·00) | 0 (0·00) |
| Injection site swelling | 5 (4·95) | 0 (0·00) | 11 (10.58) | 2 (3·92) | 0 (0·00) |
| Adverse Events after the 2nd vaccination, n (%) | | | | | |
| Injection site pain | 79 (78·22) | 4 (40·00) | 89 (85·58) | 24 (47·06) | 8 (13·11) |
| Injection site redness | 7 (6·93) | 0 (0·00) | 10 (9·62) | 0 (0·00) | 0 (0·00) |
| Injection site swelling | 9 (8·91) | 0 (0·00) | 8 (7·69) | 0 (0·00) | 0 (0·00) |

%: n / (No. of participant in Safety Set by group) * 100
95% Confidence Interval for the percentage of participants with AE is calculated by Clopper-Pearson Methods.
n: number of participants

**Table S4. Solicited systemic adverse events - number of participants experiencing the events (safety set)**

| | 10µg GBP510 with AS03 (N = 101) | 10µg GBP510 (N = 10) | 25µg GBP510 with AS03 (N = 104) | 25µg GBP510 (N = 51) | Placebo (N = 61) |
|---|---|---|---|---|---|
| Adverse Events after any vaccine injection, n (%) | | | | | |
| Fever | 10 (9·90) | 0 (0·00) | 18 (17·31) | 0 (0·00) | 1 (1·64) |
| Nausea/vomiting | 18 (17·82) | 2 (20·00) | 24 (23·08) | 3 (5·88) | 6 (9·84) |
| Diarrhea | 18 (17·82) | 2 (20·00) | 17 (16·35) | 9 (17·65) | 5 (8·20) |
| Headache | 54 (53·47) | 4 (40·00) | 59 (56·73) | 16 (31·37) | 21 (34·43) |
| Fatigue | 80 (79·21) | 4 (40·00) | 78 (75·00) | 31 (60·78) | 30 (49·18) |
| Myalgia | 79 (78·22) | 4 (40·00) | 83 (79·81) | 24 (47·06) | 19 (31·15) |
| Arthralgia | 39 (38·61) | 1 (10·00) | 42 (40·38) | 11 (21·57) | 10 (16·39) |
| Chills | 44 (43·56) | 1 (10·00) | 57 (54·81) | 4 (7·84) | 10 (16·39) |
| Adverse events after the first dose, n (%) | | | | | |
| Fever | 0 (0·00) | 0 (0·00) | 2 (1·92) | 0 (0·00) | 1 (1·64) |
| Nausea/vomiting | 6 (5·94) | 1 (10·00) | 9 (8·65) | 1 (1·96) | 3 (4·92) |
| Diarrhea | 9 (8·91) | 2 (20·00) | 11 (10·58) | 5 (9·80) | 4 (6·56) |
| Headache | 24 (23·76) | 3 (30·00) | 26 (25·00) | 10 (19·61) | 12 (19·67) |
| Fatigue | 56 (55·45) | 3 (30·00) | 54 (51·92) | 24 (47·06) | 25 (40·98) |
| Myalgia | 54 (53·47) | 2 (20·00) | 55 (52·88) | 19 (37·25) | 13 (21·31) |
| Arthralgia | 20 (19·80) | 1 (10·00) | 21 (20·19) | 6 (11·76) | 3 (4·92) |
| Chills | 11 (10·89) | 1 (10·00) | 14 (13·46) | 4 (7·84) | 1 (1·64) |
| Adverse events after the second dose, n (%) | | | | | |
| Fever | 10 (9·90) | 0 (0·00) | 17 (16·35) | 0 (0·00) | 0 (0·00) |
| Nausea/vomiting | 14 (13·86) | 1 (10·00) | 19 (18·27) | 3 (5·88) | 3 (4·92) |
| Diarrhea | 12 (11·88) | 0 (0·00) | 9 (8·65) | 6 (11·76) | 2 (3·28) |
| Headache | 46 (45·54) | 2 (20·00) | 52 (50·00) | 10 (19·61) | 13 (21·31) |
| Fatigue | 69 (68·32) | 2 (20·00) | 77 (74·04) | 22 (43·14) | 24 (39·34) |

| | | | | | |
|---|---|---|---|---|---|
| Myalgia | 68 (67·33) | 3 (30·00) | 76 (73·08) | 15 (29·41) | 11 (18·03) |
| Arthralgia | 33 (32·67) | 0 (0·00) | 36 (34·62) | 5 (9·80) | 8 (13·11) |
| Chills | 41 (40·59) | 0 (0·00) | 53 (50·96) | 1 (1·96) | 10 (16·39) |

%: n / (No. of participant in Safety Set by group) * 100
95% Confidence Interval for the percentage of participants with AE is calculated by Clopper-Pearson Methods.
n: number of participants

**Table S5. Hematologic laboratory monitoring for adverse events through 28 days after second-dose vaccination (safety set)**

| Screening | 10µg GBP510 with AS03 (N = 101) | | 10µg GBP510 (N = 10) | | 25µg GBP510 with AS03 (N = 104) | | 25µg GBP510 (N = 51) | | Placebo (N = 61) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Normal/NCS | CS | Normal/NCS | CS | Normal/NCS | CS | Normal/NCS | CS | Normal/NCS | CS |
| WBC, n (%) | | | | | | | | | | |
| Normal/NCS | 97 (98·98) | 1 (1·02) | 10 (100·00) | 0 (0·00) | 103 (100·00) | 0 (0·00) | 49 (100·00) | 0 (0·00) | 60 (100·00) | 0 (0·00) |
| CS | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |
| RBC, n (%) | | | | | | | | | | |
| Normal/NCS | 98 (100·00) | 0 (0·00) | 10 (100·00) | 0 (0·00) | 103 (100·00) | 0 (0·00) | 49 (100·00) | 0 (0·00) | 60 (100·00) | 0 (0·00) |
| CS | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |
| Hemoglobin, n (%) | | | | | | | | | | |
| Normal/NCS | 98 (100·00) | 0 (0·00) | 10 (100·00) | 0 (0·00) | 103 (100·00) | 0 (0·00) | 49 (100·00) | 0 (0·00) | 60 (100·00) | 0 (0·00) |
| CS | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |
| Hematocrit, n (%) | | | | | | | | | | |
| Normal/NCS | 98 (100·00) | 0 (0·00) | 10 (100·00) | 0 (0·00) | 103 (100·00) | 0 (0·00) | 49 (100·00) | 0 (0·00) | 60 (100·00) | 0 (0·00) |
| CS | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |
| Platelet, n (%) | | | | | | | | | | |
| Normal/NCS | 98 (100·00) | 0 (0·00) | 10 (100·00) | 0 (0·00) | 103 (100·00) | 0 (0·00) | 49 (100·00) | 0 (0·00) | 60 (100·00) | 0 (0·00) |
| CS | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |
| Neutrophil, n (%) | | | | | | | | | | |
| Normal/NCS | 98 (100·00) | 0 (0·00) | 10 (100·00) | 0 (0·00) | 103 (100·00) | 0 (0·00) | 49 (100·00) | 0 (0·00) | 60 (100·00) | 0 (0·00) |
| CS | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |
| Lymphocytes, n (%) | | | | | | | | | | |
| Normal/NCS | 98 (100·00) | 0 (0·00) | 10 (100·00) | 0 (0·00) | 103 (100·00) | 0 (0·00) | 49 (100·00) | 0 (0·00) | 60 (100·00) | 0 (0·00) |
| CS | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |
| Eosinophils, n (%) | | | | | | | | | | |
| Normal/NCS | 98 (100·00) | 0 (0·00) | 10 (100·00) | 0 (0·00) | 103 (100·00) | 0 (0·00) | 49 (100·00) | 0 (0·00) | 59 (98·33) | 1 (1·67) |
| CS | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |

NCS, not clinically significant abnormal; CS, clinically significant abnormal
Participants evaluated both screening and visit 7 were analysed.
%: n / (No. of participants in each group) * 100; it is calculated based on the total number of participants who were available on visit 7.
n: number of participants

**Table S6. Blood biochemistry test monitoring for adverse events through 28 days after second-dose vaccination (safety set)**

| Screening | 10μg GBP510 with AS03 (N = 101) | | 10μg GBP510 (N = 10) | | 25μg GBP510 with AS03 (N = 104) | | 25μg GBP510 (N = 51) | | Placebo (N = 61) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Normal/NCS | CS | Normal/NCS | CS | Normal/NCS | CS | Normal/NCS | CS | Normal/NCS | CS |
| Glucose, n (%) | | | | | | | | | | |
| Normal/NCS | 98 (100·00) | 0 (0·00) | 10 (100·00) | 0 (0·00) | 103 (100·00) | 0 (0·00) | 49 (100·00) | 0 (0·00) | 60 (100·00) | 0 (0·00) |
| CS | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |
| Aspartate transaminase (AST), n (%) | | | | | | | | | | |
| Normal/NCS | 98 (100·00) | 0 (0·00) | 10 (100·00) | 0 (0·00) | 103 (100·00) | 0 (0·00) | 49 (100·00) | 0 (0·00) | 59 (98·33) | 1 (1·67) |
| CS | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |
| Alanine transferase (ALT), n (%) | | | | | | | | | | |
| Normal/NCS | 97 (98·98) | 1 (1·02) | 10 (100·00) | 0 (0·00) | 103 (100·00) | 0 (0·00) | 49 (100·00) | 0 (0·00) | 59 (98·33) | 1 (1·67) |
| CS | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |
| Alkaline phosphatase (ALP), n (%) | | | | | | | | | | |
| Normal/NCS | 98 (100·00) | 0 (0·00) | 10 (100·00) | 0 (0·00) | 103 (100·00) | 0 (0·00) | 49 (100·00) | 0 (0·00) | 60 (100·00) | 0 (0·00) |
| CS | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |
| Total bilirubin, n (%) | | | | | | | | | | |
| Normal/NCS | 98 (100·00) | 0 (0·00) | 10 (100·00) | 0 (0·00) | 103 (100·00) | 0 (0·00) | 49 (100·00) | 0 (0·00) | 60 (100·00) | 0 (0·00) |
| CS | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |
| Total protein, n (%) | | | | | | | | | | |
| Normal/NCS | 98 (100·00) | 0 (0·00) | 10 (100·00) | 0 (0·00) | 103 (100·00) | 0 (0·00) | 49 (100·00) | 0 (0·00) | 60 (100·00) | 0 (0·00) |
| CS | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |
| Albumin, n (%) | | | | | | | | | | |
| Normal/NCS | 98 (100·00) | 0 (0·00) | 10 (100·00) | 0 (0·00) | 103 (100·00) | 0 (0·00) | 49 (100·00) | 0 (0·00) | 60 (100·00) | 0 (0·00) |
| CS | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |
| BUN, n (%) | | | | | | | | | | |
| Normal/NCS | 98 (100·00) | 0 (0·00) | 10 (100·00) | 0 (0·00) | 103 (100·00) | 0 (0·00) | 49 (100·00) | 0 (0·00) | 60 (100·00) | 0 (0·00) |
| CS | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |
| Creatinine, n (%) | | | | | | | | | | |
| Normal/NCS | 98 (100·00) | 0 (0·00) | 10 (100·00) | 0 (0·00) | 103 (100·00) | 0 (0·00) | 49 (100·00) | 0 (0·00) | 60 (100·00) | 0 (0·00) |
| CS | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |
| Uric acid, n (%) | | | | | | | | | | |
| Normal/NCS | 98 (100·00) | 0 (0·00) | 10 (100·00) | 0 (0·00) | 103 (100·00) | 0 (0·00) | 49 (100·00) | 0 (0·00) | 59 (98·33) | 1 (1·67) |

| Screening | 10µg GBP510 with AS03 (N = 101) | | 10µg GBP510 (N = 10) | | 25µg GBP510 with AS03 (N = 104) | | 25µg GBP510 (N = 51) | | Placebo (N = 61) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Normal/NCS | CS | Normal/NCS | CS | Normal/NCS | CS | Normal/NCS | CS | Normal/NCS | CS |
| CS | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |
| Total cholesterol, n (%) | | | | | | | | | | |
| Normal/NCS | 98 (100·00) | 0 (0·00) | 10 (100·00) | 0 (0·00) | 103 (100·00) | 0 (0·00) | 48 (97·96) | 1 (2·04) | 60 (100·00) | 0 (0·00) |
| CS | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |
| Triglyceride, n (%) | | | | | | | | | | |
| Normal/NCS | 95 (96·94) | 0 (0·00) | 10 (100·00) | 0 (0·00) | 100 (97·09) | 3 (2·91) | 49 (100·00) | 0 (0·00) | 59 (98·33) | 1 (1·67) |
| CS | 3 (3·06) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |
| Calcium, n (%) | | | | | | | | | | |
| Normal/NCS | 98 (100·00) | 0 (0·00) | 10 (100·00) | 0 (0·00) | 103 (100·00) | 0 (0·00) | 49 (100·00) | 0 (0·00) | 60 (100·00) | 0 (0·00) |
| CS | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |
| Phosphorus, n (%) | | | | | | | | | | |
| Normal/NCS | 98 (100·00) | 0 (0·00) | 10 (100·00) | 0 (0·00) | 103 (100·00) | 0 (0·00) | 49 (100·00) | 0 (0·00) | 60 (100·00) | 0 (0·00) |
| CS | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |
| Sodium, n (%) | | | | | | | | | | |
| Normal/NCS | 98 (100·00) | 0 (0·00) | 10 (100·00) | 0 (0·00) | 103 (100·00) | 0 (0·00) | 49 (100·00) | 0 (0·00) | 60 (100·00) | 0 (0·00) |
| CS | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |
| Potassium, n (%) | | | | | | | | | | |
| Normal/NCS | 98 (100·00) | 0 (0·00) | 10 (100·00) | 0 (0·00) | 103 (100·00) | 0 (0·00) | 49 (100·00) | 0 (0·00) | 60 (100·00) | 0 (0·00) |
| CS | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |

NCS, not clinically significant abnormal; CS, clinically significant abnormal; BUN, blood urea nitrogen

Participants evaluated at both screening and visit 7 were analysed.

%: n / (No. of participants in each group) * 100; it is calculated based on the total number of participants who were available on visit 7.

n: number of participants

**Table S7. Unsolicited adverse events by category (safety set)**

| | 10µg GBP510 with AS03 (N = 101) | 10µg GBP510 (N = 10) | 25µg GBP510 with AS03 (N = 104) | 25µg GBP510 (N = 51) | Placebo (N = 61) |
|---|---|---|---|---|---|
| Adverse events after any vaccine injection | | | | | |
| Total number of AE occurrences (n) | 26 | 3 | 31 | 16 | 16 |
| Maximum severity, No· of AEs (%) | | | | | |
| Grade 1 (mild) | 21 (80·77) | 1 (33·33) | 18 (58·06) | 13 (81·25) | 14 (87·50) |
| Grade 2 (moderate) | 3 (11·54) | 2 (66·67) | 11 (35·48) | 3 (18·75) | 2 (12·50) |
| Grade 3 (severe) | 2 (7·69) | 0 (0·00) | 2 (6·45) | 0 (0·00) | 0 (0·00) |
| Grade 4 (life threatening) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |
| Seriousness, number of AEs (%) | | | | | |
| Yes | 0 (0·00) | 0 (0·00) | 1 (3·23) | 2 (12·50) | 0 (0·00) |
| No | 26 (100·00) | 3 (100·00) | 30 (96·77) | 14 (87·50) | 16 (100·00) |
| Outcome, number of AEs (%) | | | | | |
| Recovered/resolved | 21 (80·77) | 3 (100·00) | 29 (93·55) | 12 (75·00) | 15 (93·75) |
| Recovering/resolving | 3 (11·54) | 0 (0·00) | 1 (3·23) | 2 (12·50) | 1 (6·25) |
| Not recovered/not resolved | 2 (7·69) | 0 (0·00) | 1 (3·23) | 1 (6·25) | 0 (0·00) |
| Stabilised | 1 (3·85) | 0 (0·00) | 1 (3·23) | 1 (6·25) | 0 (0·00) |
| Not stabilised | 1 (3·85) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |
| Recovered/resolved with sequelae | 0 (0·00) | 0 (0·00) | 0 (0·00) | 1 (6·25) | 0 (0·00) |
| Fatal | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |
| Unknown | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |
| Causality, number of AEs (%) | | | | | |
| Related | 7 (26·92) | 0 (0·00) | 9 (29·03) | 4 (25·00) | 2 (12·50) |
| Not-related | 19 (73·08) | 3 (100·00) | 22 (70·97) | 12 (75·00) | 14 (87·50) |
| Action taken with IP, No· of AEs (%) | | | | | |
| Stop vaccination | 0 (0·00) | 0 (0·00) | 0 (0·00) | 4 (25·00) | 0 (0·00) |
| Continue to vaccination | 12 (46·15) | 2 (66·67) | 17 (54·84) | 7 (43·75) | 7 (43·75) |
| Unknown | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |
| Not applicable | 14 (53·85) | 1 (33·33) | 14 (45·16) | 5 (31·25) | 9 (56·25) |
| Medication (including other treatment), number of AEs (%) | | | | | |
| Yes | 15 (57·69) | 2 (66·67) | 18 (58·06) | 12 (75·00) | 10 (62·50) |
| No | 11 (42·31) | 1 (33·33) | 13 (41·94) | 4 (25·00) | 6 (37·50) |
| Immediate systemic reaction, number of AEs (%) | | | | | |
| Yes | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |
| No | 26 (100·00) | 3 (100·00) | 31 (100·00) | 16 (100·00) | 16 (100·00) |

| | 10μg GBP510 with AS03 (N = 101) | 10μg GBP510 (N = 10) | 25μg GBP510 with AS03 (N = 104) | 25μg GBP510 (N = 51) | Placebo (N = 61) |
|---|---|---|---|---|---|
| MAAE, number of AEs (%) | | | | | |
| Yes | 12 (46·15) | 2 (66·67) | 9 (29·03) | 8 (50·00) | 5 (31·25) |
| Hospitalization | 0 (0·00) | 0 (0·00) | 1 (3·23) | 1 (6·25) | 0 (0·00) |
| ER visit | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |
| Other visit to a healthcare professional | 12 (46·15) | 2 (66·67) | 8 (25·81) | 7 (43·75) | 5 (31·25) |
| No | 14 (53·85) | 1 (33·33) | 22 (70·97) | 8 (50·00) | 11 (68·75) |
| AESI, number of AEs (%) | | | | | |
| Yes | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |
| No | 26 (100·00) | 3 (100·00) | 31 (100·00) | 16 (100·00) | 16 (100·00) |
| Adverse events after the 1st vaccination | | | | | |
| Total number of AE occurrences (n) | 12 | 2 | 17 | 11 | 7 |
| Maximum severity, number of AEs (%) | | | | | |
| Grade 1 (mild) | 11 (91·67) | 1 (50·00) | 9 (52·94) | 9 (81·82) | 6 (85·71) |
| Grade 2 (moderate) | 0 (0·00) | 1 (50·00) | 6 (35·29) | 2 (18·18) | 1 (14·29) |
| Grade 3 (severe) | 1 (8·33) | 0 (0·00) | 2 (11·76) | 0 (0·00) | 0 (0·00) |
| Grade 4 (life threatening) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |
| Seriousness, number of AEs (%) | | | | | |
| Yes | 0 (0·00) | 0 (0·00) | 1 (5·88) | 2 (18·18) | 0 (0·00) |
| No | 12 (100·00) | 2 (100·00) | 16 (94·12) | 9 (81·82) | 7 (100·00) |
| Outcome, number of AEs (%) | | | | | |
| Recovered/resolved | 9 (75·00) | 2 (100·00) | 17 (100·00) | 7 (63·64) | 7 (100·00) |
| Recovering/resolving | 2 (16·67) | 0 (0·00) | 0 (0·00) | 2 (18·18) | 0 (0·00) |
| Not recovered/not resolved | 1 (8·33) | 0 (0·00) | 0 (0·00) | 1 (9·09) | 0 (0·00) |
| Stabilised | 0 (0·00) | 0 (0·00) | 0 (0·00) | 1 (9·09) | 0 (0·00) |
| Not stabilised | 1 (8·33) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |
| Recovered/resolved with sequelae | 0 (0·00) | 0 (0·00) | 0 (0·00) | 1 (9·09) | 0 (0·00) |
| Fatal | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |
| Unknown | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |
| Causality, number of AEs (%) | | | | | |
| Related | 1 (8·33) | 0 (0·00) | 5 (29·41) | 4 (36·36) | 1 (14·29) |
| Not-related | 11 (91·67) | 2 (100·00) | 12 (70·59) | 7 (63·64) | 6 (85·71) |
| Action taken with IP, number of AEs (%) | | | | | |
| Stop vaccination | 0 (0·00) | 0 (0·00) | 0 (0·00) | 4 (36·36) | 0 (0·00) |
| Continue to vaccination | 12 (100·00) | 2 (100·00) | 17 (100·00) | 7 (63·64) | 7 (100·00) |
| Unknown | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |

| | 10µg GBP510 with AS03 (N = 101) | 10µg GBP510 (N = 10) | 25µg GBP510 with AS03 (N = 104) | 25µg GBP510 (N = 51) | Placebo (N = 61) |
|---|---|---|---|---|---|
| Not applicable | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |
| Medication (including other treatment), number of AEs (%) | | | | | |
| Yes | 9 (75·00) | 1 (50·00) | 11 (64·71) | 10 (90·91) | 7 (100·00) |
| No | 3 (25·00) | 1 (50·00) | 6 (35·29) | 1 (9·09) | 0 (0·00) |
| Immediate systemic reaction, number of AEs (%) | | | | | |
| Yes | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |
| No | 12 (100·00) | 2 (100·00) | 17 (100·00) | 11 (100·00) | 7 (100·00) |
| MAAE, number of AEs (%) | | | | | |
| Yes | 5 (41·67) | 2 (100·00) | 6 (35·29) | 7 (63·64) | 2 (28·57) |
| Hospitalization | 0 (0·00) | 0 (0·00) | 1 (5·88) | 1 (9·09) | 0 (0·00) |
| ER visit | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |
| Other visit to a healthcare professional | 5 (41·67) | 2 (100·00) | 5 (29·41) | 6 (54·55) | 2 (28·57) |
| No | 7 (58·33) | 0 (0·00) | 11 (64·71) | 4 (36·36) | 5 (71·43) |
| AESI, number of AEs (%) | | | | | |
| Yes | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |
| No | 12 (100·00) | 2 (100·00) | 17 (100·00) | 11 (100·00) | 7 (100·00) |
| Adverse events after the 2nd vaccination | | | | | |
| Total number of AE occurrences (n) | 14 | 1 | 14 | 5 | 9 |
| Maximum severity, number of AEs (%) | | | | | |
| Grade 1 (mild) | 10 (71·43) | 0 (0·00) | 9 (64·29) | 4 (80·00) | 8 (88·89) |
| Grade 2 (moderate) | 3 (21·43) | 1 (100·00) | 5 (35·71) | 1 (20·00) | 1 (11·11) |
| Grade 3 (severe) | 1 (7·14) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |
| Grade 4 (life threatening) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |
| Seriousness, number of AEs (%) | | | | | |
| Yes | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |
| No | 14 (100·00) | 1 (100·00) | 14 (100·00) | 5 (100·00) | 9 (100·00) |
| Outcome, number of AEs (%) | | | | | |
| Recovered/resolved | 12 (85·71) | 1 (100·00) | 12 (85·71) | 5 (100·00) | 8 (88·89) |
| Recovering/resolving | 1 (7·14) | 0 (0·00) | 1 (7·14) | 0 (0·00) | 1 (11·11) |
| Not recovered/not resolved | 1 (7·14) | 0 (0·00) | 1 (7·14) | 0 (0·00) | 0 (0·00) |
| Stabilised | 1 (7·14) | 0 (0·00) | 1 (7·14) | 0 (0·00) | 0 (0·00) |
| Not stabilised | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |
| Recovered/resolved with sequelae | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |
| Fatal | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |
| Unknown | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |

| | 10µg GBP510 with AS03 (N = 101) | 10µg GBP510 (N = 10) | 25µg GBP510 with AS03 (N = 104) | 25µg GBP510 (N = 51) | Placebo (N = 61) |
|---|---|---|---|---|---|
| Causality, number of AEs (%) | | | | | |
| Related | 6 (42·86) | 0 (0·00) | 4 (28·57) | 0 (0·00) | 1 (11·11) |
| Not-related | 8 (57·14) | 1 (100·00) | 10 (71·43) | 5 (100·00) | 8 (88·89) |
| Action taken with IP, number of AEs (%) | | | | | |
| Stop vaccination | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |
| Continue to vaccination | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |
| Unknown | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |
| Not applicable | 14 (100·00) | 1 (100·00) | 14 (100·00) | 5 (100·00) | 9 (100·00) |
| Medication (including other treatment), number of AEs (%) | | | | | |
| Yes | 6 (42·86) | 1 (100·00) | 7 (50·00) | 2 (40·00) | 3 (33·33) |
| No | 8 (57·14) | 0 (0·00) | 7 (50·00) | 3 (60·00) | 6 (66·67) |
| Immediate systemic reaction, number of AEs (%) | | | | | |
| Yes | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |
| No | 14 (100·00) | 1 (100·00) | 14 (100·00) | 5 (100·00) | 9 (100·00) |
| MAAE, number of AEs (%) | | | | | |
| Yes | 7 (50·00) | 0 (0·00) | 3 (21·43) | 1 (20·00) | 3 (33·33) |
| Hospitalization | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |
| ER visit | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |
| Other visit to a healthcare professional | 7 (50·00) | 0 (0·00) | 3 (21·43) | 1 (20·00) | 3 (33·33) |
| No | 7 (50·00) | 1 (100·00) | 11 (78·57) | 4 (80·00) | 6 (66·67) |
| AESI, number of AEs (%) | | | | | |
| Yes | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) | 0 (0·00) |
| No | 14 (100·00) | 1 (100·00) | 14 (100·00) | 5 (100·00) | 9 (100·00) |

AEs, adverse events; SAE, serious adverse events; MAAE, medically attended adverse events; adverse events of special interest (AESIs); MAADRS, medically attended adverse drug reactions; IP, investigational product; ER, emergency room.
%: n / (No. of AEs in Safety Set by group) * 100
n: number of AE

**Table S8. Geometric mean concentrations and seroconversion rates of IgG antibody titer to the SARS-CoV-2-RBD (Parental D614G Strain) by enzyme-linked immunosorbent assay (per-protocol set)**

| | 10μg GBP510 with AS03 (N = 93) | 10μg GBP510 (N = 10) | 25μg GBP510 with AS03 (N = 96) | 25μg GBP510 (N = 45) | Placebo (N = 58) |
|---|---|---|---|---|---|
| Geometric mean titer and seroconversion rate | | | | | |
| Baseline | | | | | |
| n | 93 | 10 | 96 | 45 | 58 |
| GMC ± standard deviation (BAU/mL) | 15·08 ± 1·69 | 10·95 ± 1·61 | 13·85 ± 1·72 | 16·34 ± 1·66 | 12·51 ± 1·64 |
| 95% CI (lower, upper) | (13·54, 16·80) | (7·78, 15·40) | (12·42, 15·46) | (14·04, 19·03) | (10·97, 14·25) |
| P-value vs. placebo | 0·0311 | 0·4339 | 0·2422 | 0·0084 | |
| P-value vs. GBP510 10μg with AS03 | | 0·0671 | 0·2750 | | |
| P-value vs. GBP510 25μg with AS03 | | | | 0·0862 | |
| Visit 4 (4 weeks post-1st vaccination) | | | | | |
| n | 93 | 10 | 96 | 45 | 58 |
| GMC ± standard deviation (BAU/mL) | 111·85 ± 2·10 | 37·72 ± 2·03 | 129·00 ± 2·09 | 28·63 ± 1·72 | 12·71 ± 1·71 |
| 95% CI (lower, upper) | (96·00, 130·31) | (22·74, 62·56) | (111·05, 149·84) | (24·32, 33·71) | (11·04, 14·63) |
| P-value vs. placebo | <0·0001 | <0·0001 | <0·0001 | <0·0001 | |
| P-value vs. GBP510 10μg with AS03 | | <0·0001 | 0·1871 | | |
| P-value vs. GBP510 25μg with AS03 | | | | <0·0001 | |
| GMFR ± standard deviation | 7·42 ± 2·48 | 3·45 ± 1·91 | 9·31 ± 2·34 | 1·75 ± 1·94 | 1·02 ± 1·90 |
| 95% CI (lower, upper) | (6·15, 8·94) | (2·17, 5·47) | (7·84, 11·06) | (1·44, 2·14) | (0·86, 1·20) |
| P-value vs. placebo | <0·0001 | <0·0001 | <0·0001 | <0·0001 | |
| P-value vs. GBP510 10μg with AS03 | | 0·0110 | 0·0774 | | |
| P-value vs. GBP510 25μg with AS03 | | | | <0·0001 | |
| SCR, n (%) | 68 (73·12) | 4 (40·00) | 79 (82·29) | 5 (11·11) | 0 (0·00) |
| 95% CI (lower, upper) | (62·92, 81·79) | (12·16, 73·76) | (73·17, 89·33) | (3·71, 24·05) | (0·00, 6·16) |
| P-value vs. placebo | <0·0001 | 0·0003 | <0·0001 | 0·0140 | |
| P-value vs. GBP510 10μg with AS03 | | 0·0624 | 0·1294 | | |
| P-value vs. GBP510 25μg with AS03 | | | | <0·0001 | |
| Visit 6 (2 weeks post-2nd vaccination) | | | | | |
| n | 93 | 10 | 96 | 45 | 58 |
| GMC ± standard deviation (BAU/mL) | 2,163·59 ± 1·89 | 155·30 ± 3·05 | 2,599·22 ± 1·86 | 112·40 ± 2·75 | 10·56 ± 1·63 |
| 95% CI (lower, upper) | (1,898·11, 2,466·20) | (70·02, 344·47) | (2,292·62, 2,946·83) | (82·92, 152·37) | (9·28, 12·01) |

| | 10µg GBP510 with AS03 (N = 93) | 10µg GBP510 (N = 10) | 25µg GBP510 with AS03 (N = 96) | 25µg GBP510 (N = 45) | Placebo (N = 58) |
|---|---|---|---|---|---|
| P-value vs. placebo | <0·0001 | <0·0001 | <0·0001 | <0·0001 | |
| P-value vs. GBP510 10µg with AS03 | | <0·0001 | 0·0459 | | |
| P-value vs. GBP510 25µg with AS03 | | | | <0·0001 | |
| | | | | | |
| GMFR ± standard deviation | 143·47 ± 2·33 | 14·19 ± 2·58 | 187·61 ± 2·09 | 6·88 ± 2·93 | 0·84 ± 1·66 |
| 95% CI (lower, upper) | (120·48, 170·85) | (7·21, 27·92) | (161·61, 217·81) | (4·98, 9·49) | (0·74, 0·96) |
| P-value vs. Placebo | <0·0001 | <0·0001 | <0·0001 | <0·0001 | |
| P-value vs. GBP510 10µg with AS03 | | <0·0001 | 0·0212 | | |
| P-value vs. GBP510 25µg with AS03 | | | | <0·0001 | |
| | | | | | |
| SCR, n (%) | 93 (100·00) | 10 (100·00) | 96 (100·00) | 29 (64·44) | 0 (0·00) |
| 95% CI (lower, upper) | (96·11, 100·00) | (69·15, 100·00) | (96·23, 100·00) | (48·78, 78·13) | (0·00, 6·16) |
| P-value vs. placebo | <0·0001 | <0·0001 | <0·0001 | <0·0001 | |
| P-value vs. GBP510 10µg with AS03 | | NA | NA | | |
| P-value vs. GBP510 25µg with AS03 | | | | <0·0001 | |
| Visit 7 (4 weeks post-2nd vaccination) | | | | | |
| n | 93 | 10 | 96 | 45 | 58 |
| GMC ± standard deviation (BAU/mL) | 1,517·87 ± 2·09 | 132·64 ± 2·76 | 1,943·44 ± 1·79 | 114·97 ± 2·74 | 12·52 ± 1·71 |
| 95% CI (lower, upper) | (1,304·70, 1,765·87) | (64·23, 273·91) | (1,727·73, 2,186·08) | (84·90, 155·68) | (10·88, 14·42) |
| P-value vs. placebo | <0·0001 | <0·0001 | <0·0001 | <0·0001 | |
| P-value vs. GBP510 10µg with AS03 | | <0·0001 | 0·0113 | | |
| P-value vs. GBP510 25µg with AS03 | | | | <0·0001 | |
| | | | | | |
| GMFR ± standard deviation | 100·65 ± 2·55 | 12·12 ± 2·37 | 140·28 ± 2·06 | 7·03 ± 2·90 | 1·00 ± 1·93 |
| 95% CI (lower, upper) | (83·03, 122·01) | (6·54, 22·47) | (121·14, 162·44) | (5·11, 9·68) | (0·84, 1·19) |
| P-value vs. placebo | <0·0001 | <0·0001 | <0·0001 | <0·0001 | |
| P-value vs. GBP510 10µg with AS03 | | <0·0001 | 0·0071 | | |
| P-value vs. GBP510 25µg with AS03 | | | | <0·0001 | |
| | | | | | |
| SCR, n (%) | 92 (98·92) | 10 (100·00) | 96 (100·00) | 28 (62·22) | 1 (1·72) |
| 95% CI (lower, upper) | (94·15, 99·97) | (69·15, 100·00) | (96·23, 100·00) | (46·54, 76·23) | (0·04, 9·24) |
| P-value vs. placebo | <0·0001 | <0·0001 | <0·0001 | <0·0001 | |
| P-value vs. GBP510 10µg with AS03 | | 1·0000 | 0·4921 | | |
| P-value vs. GBP510 25µg with AS03 | | | | <0·0001 | |

GMC, geometric mean concentrations; GMFR, geometric mean fold rise; SCR, seroconversion rate; CI, confidence interval; BAU, binding antibody unit; NA, not applicable

GMFR = GMC (each visit) / GMC (Baseline)

SCR: Percentage of participants with ≥ 4-fold rise from baseline

%: n / (No. of subject who information was collected at each visit by group) * 100

The 95% CI for GMC/GMFR is 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 for SCR is calculated by Clopper-Pearson Methods.

P-value versus placebo: p-value for difference of Treatment groups versus Placebo (continuous values are two sample t-test and categorical values are chi-square test or fisher's exact test)

P-value versus GBP510 10µg with AS03: p-value for difference of each group versus GBP510 10µg with AS03 (continuous values are two sample t-test and categorical values are chi-square test or fisher's exact test)

P-value versus GBP510 25µg with AS03: p-value for difference of each group versus GBP510 25µg with AS03 (continuous values are two sample t-test and categorical values are chi-square test or fisher's exact test)

n: number of participants

**Table S9. Geometric mean titers and seroconversion rates of neutralising antibody to the SARS-CoV-2 (D614G Strain) by pseudovirus-based neutralisation assay (per-protocol set)**

| | 10μg GBP510 with AS03 (N = 93) | 10μg GBP510 (N = 10) | 25μg GBP510 with AS03 (N = 96) | 25μg GBP510 (N = 45) | Placebo (N = 58) |
|---|---|---|---|---|---|
| Geometric mean titer and seroconversion rate | | | | | |
| Baseline | | | | | |
| n | 93 | 10 | 96 | 45 | 58 |
| GMT ± standard deviation (IU/mL) | 18·05 ± 1·28 | 21·01 ± 1·58 | 19·49 ± 1·43 | 19·05 ± 1·48 | 19·19 ± 1·51 |
| 95% CI (lower, upper) | (17·16, 18·99) | (15·16, 29·12) | (18·13, 20·95) | (16·94, 21·43) | (17·21, 21·39) |
| P-value vs. placebo | 0·3126 | 0·5302 | 0·8043 | 0·9290 | |
| P-value vs. GBP510 10μg with AS03 | | 0·3266 | 0·0869 | | |
| P-value vs. GBP510 25μg with AS03 | | | | 0·7321 | |
| Visit 4 (4 weeks post-1st vaccination) | | | | | |
| n | 93 | 10 | 96 | 45 | 58 |
| GMT± standard deviation (IU/mL) | 39·97 ± 2·73 | 32·79 ± 2·45 | 40·94 ± 2·77 | 21·23 ± 1·65 | 19·71 ± 1·58 |
| 95% CI (lower, upper) | (32·51, 49·14) | (17·28, 62·23) | (33·31, 50·32) | (18·28, 24·65) | (17·48, 22·22) |
| P-value vs. placebo | <0·0001 | 0·1095 | <0·0001 | 0·4327 | |
| P-value vs. GBP510 10μg with AS03 | | 0·5509 | 0·8705 | | |
| P-value vs. GBP510 25μg with AS03 | | | | <0·0001 | |
| GMFR ± standard deviation | 2·21 ± 2·78 | 1·56 ± 2·42 | 2·10 ± 2·92 | 1·11 ± 1·63 | 1·03 ± 1·91 |
| 95% CI (lower, upper) | (1·79, 2·73) | (0·83, 2·94) | (1·69, 2·61) | (0·96, 1·29) | (0·87, 1·22) |
| P-value vs. placebo | <0·0001 | 0·0776 | <0·0001 | 0·4822 | |
| P-value vs. GBP510 10μg with AS03 | | 0·3011 | 0·7307 | | |
| P-value vs. GBP510 25μg with AS03 | | | | <0·0001 | |
| SCR, n (%) | 28 (30·11) | 1 (10·00) | 27 (28·13) | 2 (4·44) | 4 (6·90) |
| 95% CI (lower, upper) | (21·03, 40·50) | (0·25, 44·50) | (19·42, 38·22) | (0·54, 15·15) | (1·91, 16·73) |
| P-value vs. placebo | 0·0007 | 0·5604 | 0·0015 | 0·6938 | |
| P-value vs. GBP510 10μg with AS03 | | 0·2754 | 0·7642 | | |
| P-value vs. GBP510 25μg with AS03 | | | | 0·0012 | |
| Visit 6 (2 weeks post-2nd vaccination) | | | | | |
| n | 93 | 10 | 96 | 45 | 58 |
| GMT ± standard deviation (IU/mL) | 1,369·02 ± 2·60 | 83·47 ± 4·47 | 1,431·45 ± 2·69 | 63·85 ± 3·31 | 19·24 ± 1·47 |
| 95% CI (lower, upper) | (1,124·49, 1,666·73) | (28·62, 243·48) | (1,171·07, 1,749·73) | (44·55, 91·50) | (17·37, 21·31) |

| | 10µg GBP510 with AS03 (N = 93) | 10µg GBP510 (N = 10) | 25µg GBP510 with AS03 (N = 96) | 25µg GBP510 (N = 45) | Placebo (N = 58) |
|---|---|---|---|---|---|
| P-value vs. placebo | <0·0001 | 0·0127 | <0·0001 | <0·0001 | |
| P-value vs. GBP510 10µg with AS03 | | 0·0002 | 0·7533 | | |
| P-value vs. GBP510 25µg with AS03 | | | | <0·0001 | |
| | | | | | |
| GMFR ± Standard deviation | 75·83 ± 2·68 | 3·97 ± 4·09 | 73·44 ± 2·88 | 3·35 ± 3·44 | 1·00 ± 1·64 |
| 95% CI (lower, upper) | (61·91, 92·88) | (1·45, 10·88) | (59·30, 90·97) | (2·31, 4·86) | (0·88, 1·14) |
| P-value vs. placebo | <0·0001 | 0·0129 | <0·0001 | <0·0001 | |
| P-value vs. GBP510 10µg with AS03 | | <0·0001 | 0·8300 | | |
| P-value vs. GBP510 25µg with AS03 | | | | <0·0001 | |
| | | | | | |
| SCR, n (%) | 93 (100·00) | 5 (50·00) | 95 (98·96) | 23 (51·11) | 1 (1·72) |
| 95% CI (lower, upper) | (96·11, 100·00) | (18·71, 81·29) | (94·33, 99·97) | (35·77, 66·30) | (0·04, 9·24) |
| P-value vs. placebo | <0·0001 | 0·0001 | <0·0001 | <0·0001 | |
| P-value vs. GBP510 10µg with AS03 | | <0·0001 | 1·0000 | | |
| P-value vs. GBP510 25µg with AS03 | | | | <0·0001 | |
| Visit 7 (4 weeks post-2nd vaccination) | | | | | |
| n | 93 | 10 | 96 | 45 | 58 |
| GMT ± standard deviation (IU/mL) | 838·79 ± 2·74 | 68·52 ± 3·85 | 1,107·32 ± 2·61 | 51·87 ± 3·36 | 19·29 ± 1·49 |
| 95% CI (lower, upper) | (681·68, 1,032·11) | (26·12, 179·79) | (911·43, 1,345·31) | (36·05, 74·63) | (17·38, 21·41) |
| P-value vs. placebo | <0·0001 | 0·0157 | <0·0001 | <0·0001 | |
| P-value vs. GBP510 10µg with AS03 | | <0·0001 | 0·0539 | | |
| P-value vs. GBP510 25µg with AS03 | | | | <0·0001 | |
| | | | | | |
| GMFR ± Standard deviation | 46·46 ± 2·78 | 3·26 ± 4·15 | 56·81 ± 2·95 | 2·72 ± 3·72 | 1·01 ± 1·72 |
| 95% CI (lower, upper) | (37·62, 57·37) | (1·18, 9·02) | (45·64, 70·72) | (1·84, 4·04) | (0·87, 1·16) |
| P-value vs. placebo | <0·0001 | 0·0284 | <0·0001 | <0·0001 | |
| P-value vs. GBP510 10µg with AS03 | | <0·0001 | 0·1909 | | |
| P-value vs. GBP510 25µg with AS03 | | | | <0·0001 | |
| | | | | | |
| SCR, n (%) | 91 (97·85) | 5 (50·00) | 95 (98·96) | 19 (42·22) | 2 (3·45) |
| 95% CI (lower, upper) | (92·45, 99·74) | (18·71, 81·29) | (94·33, 99·97) | (27·66, 57·85) | (0·42, 11·91) |
| P-value vs. placebo | <0·0001 | 0·0004 | <0·0001 | <0·0001 | |
| P-value vs. GBP510 10µg with AS03 | | <0·0001 | 0·6171 | | |
| P-value vs. GBP510 25µg with AS03 | | | | <0·0001 | |

GMT, geometric mean titer; GMFR, geometric mean fold rise; SCR, seroconversion rate; CI, confidence interval

GMFR = GMT (each visit) / GMT (Baseline)

SCR: Percentage of participants with ≥ 4-fold rise from baseline

%: n / (No· of participant who information was collected at each visit by group) * 100

The 95% CI for GMT/GMFR is 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 for SCR is calculated by Clopper-Pearson Methods.

P-value versus placebo: p-value for difference of Treatment groups versus Placebo (continuous values are two sample t-test and categorical values are chi-square test or fisher's exact test)

P-value versus GBP510 10µg with AS03: p-value for difference of each group versus GBP510 10µg with AS03 (continuous values are two sample t-test and categorical values are chi-square test or fisher's exact test)

P-value versus GBP510 25µg with AS03: p-value for difference of each group versus GBP510 25µg with AS03 (continuous values are two sample t-test and categorical values are chi-square test or fisher's exact test)

Strain used in PBNA: SARS-CoV-2/Wuhan-Hu-1/surface glycoprotein/ID: NC_045512.2

**Table S10. Geometric mean titers and seroconversion rates of neutralising antibody to the SARS-CoV-2 (Parental D614G Strain) by plaque reduction neutralisation test (per-protocol set)**

| | 10µg GBP510 with AS03 (N = 93) | 10µg GBP510 (N = 10) | 25µg GBP510 with AS03 (N = 96) | 25µg GBP510 (N = 45) | Placebo (N = 58) |
|---|---|---|---|---|---|
| Geometric mean titer and seroconversion rate | | | | | |
| Baseline | | | | | |
| N | 23 | 4 | 21 | 9 | 19 |
| GMT ± Standard deviation (IU/mL) | 4·40±1·71 | 9·00±1·00 | 4·33±1·70 | 4·33±1·73 | 4·76±1·75 |
| 95% CI (lower, upper) | (3·49, 5·54) | (9·00, 9·00) | (3·40, 5·51) | (2·84, 6·60) | (3·64, 6·23) |
| P-value vs. Placebo | 0·6367 | <0·0001 | 0·5787 | 0·6713 | |
| P-value vs. GBP510 10µg with AS03 | | <0·0001 | 0·9216 | | |
| P-value vs. GBP510 25µg with AS03 | | | | 1·0000 | |
| Visit 6 (2 weeks post-2nd vaccination) | | | | | |
| N | 23 | 4 | 21 | 9 | 19 |
| GMT ± Standard deviation (IU/mL) | 949·84±2·24 | 34·08±6·05 | 860·96±1·86 | 58·13±5·09 | 4·76±1·75 |
| 95% CI (lower, upper) | (670·40, 1,345·77) | (1·94, 597·40) | (649·60, 1,141·10) | (16·64, 203·13) | (3·64, 6·23) |
| P-value vs. Placebo | <0·0001 | 0·1156 | <0·0001 | 0·0016 | |
| P-value vs. GBP510 10µg with AS03 | | 0·0320 | 0·6548 | | |
| P-value vs. GBP510 25µg with AS03 | | | | 0·0009 | |
| GMFR ± Standard deviation | 216·06±2·04 | 3·79±6·05 | 198·99±1·83 | 13·44±4·50 | 1·00±1·00 |
| 95% CI (lower, upper) | (158·81, 293·95) | (0·22, 66·38) | (151·17, 261·93) | (4·23, 42·71) | (1·00, 1·00) |
| P-value vs. Placebo | <0·0001 | 0·2356 | <0·0001 | 0·0008 | |
| P-value vs. GBP510 10µg with AS03 | | 0·0190 | 0·6827 | | |
| P-value vs. GBP510 25µg with AS03 | | | | 0·0005 | |
| SCR, n (%) | 23 (100·00) | 2 (50·00) | 21 (100·00) | 7 (77·78) | 0 (0·00) |
| 95% CI (lower, upper) | (85·18, 100·00) | (6·76, 93·24) | (83·89, 100·00) | (39·99, 97·19) | (0·00, 17·65) |
| P-value vs. Placebo | <0·0001 | 0·0237 | <0·0001 | <0·0001 | |
| P-value vs. GBP510 10µg with AS03 | | 0·0171 | NA | | |
| P-value vs. GBP510 25µg with AS03 | | | | 0·0828 | |

GMT, geometric mean titer; GMFR, geomtetric mean fold rise; SCR, seroconversion rate; CI, confidence interval
GMFR = GMT (each visit) / GMT (Baseline)
SCR: Percentage of participants with ≥ 4-fold rise from baseline
%: n / (No. of subject who information was collected at each visit by group) * 100

The 95% CI for GMT/GMFR is 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 for SCR is calculated by Clopper-Pearson Methods·

P-value vs Placebo: P-value for difference of Treatment groups versus Placebo (continuous values are two sample t-test and categorical values are chi-square test or fisher's exact test·)

P-value vs GBP510 10µg with AS03: P-value for difference of each group versus GBP510 10µg with AS03 (continuous values are two sample t-test and categorical values are chi-square test or fisher's exact test·)

P-value vs GBP510 25µg with AS03: P-value for difference of each group versus GBP510 25µg with AS03 (continuous values are two sample t-test and categorical values are chi-square test or fisher's exact test·)

n: number of participants

Strain used in PRNT: Wuhan: BetaCoV/Korea/KCDC03/2020/ID: NCCP. 43326

**Table S11. Geometric mean concentration and seroconversion rate of IgG antibody to the SARS-CoV-2-RBD (Parental D614G Strain) in adults aged 19-64 years: analysis by enzyme-linked immunosorbent assay (per-protocol set)**

| | 10μg GBP510 with AS03 (N=81) | 10μg GBP510 (N=10) | 25μg GBP510 with AS03 (N=85) | 25μg GBP510 (N=41) | Placebo (N=53) |
|---|---|---|---|---|---|
| Geometric mean titer and seroconversion rate | | | | | |
| Baseline | | | | | |
| n | 81 | 10 | 85 | 41 | 53 |
| GMC±standard deviation (BAU/mL) | 14·72±1·72 | 10·95±1·61 | 13·18±1·67 | 16·24±1·70 | 12·20±1·63 |
| 95% CI (lower, upper) | (13·06, 16·59) | (7·78, 15·40) | (11·81, 14·72) | (13·4, 19·20) | (10·66, 13·97) |
| P-value vs. Placebo | 0·0441 | 0·5220 | 0·3820 | 0·0081 | |
| P-value vs. 10μg GBP510 with AS03 | | 0·1020 | 0·1799 | | |
| P-value vs. 25μg GBP510 with AS03 | | | | 0·0360 | |
| Visit 4 (4 weeks post-1st vaccination) | | | | | |
| n | 81 | 10 | 85 | 41 | 53 |
| GMC±standard deviation (BAU/mL) | 121·33±1·94 | 37·72±2·03 | 135·87±2·03 | 29·65±1·72 | 12·66±1·71 |
| 95% CI (lower, upper) | (104·75, 140·53) | (22·74, 62·56) | (116·57, 158·37) | (24·97, 35·20) | (10·92, 14·67) |
| P-value vs. Placebo | <0·0001 | <0·0001 | <0·0001 | <0·0001 | |
| P-value vs. 10μg GBP510 with AS03 | | <0·0001 | 0·2912 | | |
| P-value vs. 25μg GBP510 with AS03 | | | | <0·0001 | |
| GMFR±standard deviation | 8·24±2·33 | 3·45±1·91 | 10·31±2·23 | 1·83±1·94 | 1·04±1·88 |
| 95% CI (lower, upper) | (6·84, 9·94) | (2·17, 5·47) | (8·67, 12·26) | (1·48, 2·25) | (0·87, 1·23) |
| P-value vs. Placebo | <0·0001 | <0·0001 | <0·0001 | <0·0001 | |
| P-value vs. 10μg GBP510 with AS03 | | 0·0023 | 0·0835 | | |
| P-value vs. 25μg GBP510 with AS03 | | | | <0·0001 | |
| SCR, n (%) | 63 (77·78) | 4 (40·00) | 75 (88·24) | 5 (12·20) | 0 (0·00) |
| 95% CI (lower, upper) | (67·17, 86·27) | (12·16, 73·76) | (79·43, 94·21) | (4·08, 26·20) | (0·00, 6·72) |
| P-value vs. Placebo | <0·0001 | 0·0004 | <0·0001 | 0·0137 | |
| P-value vs. 10μg GBP510 with AS03 | | 0·0189 | 0·0721 | | |
| P-value vs 25μg GBP510 with AS03 | | | | <0·0001 | |

| | 10µg GBP510 with AS03 (N=81) | 10µg GBP510 (N=10) | 25µg GBP510 with AS03 (N=85) | 25µg GBP510 (N=41) | Placebo (N=53) |
|---|---|---|---|---|---|
| Visit 6 (2 weeks post-2nd vaccination) | | | | | |
| n | 81 | 10 | 85 | 41 | 53 |
| GMC±standard deviation (BAU/mL) | 2,368·72±1·72 | 155·30±3·05 | 2,777·08±1·71 | 114·64±2·69 | 10·37±1·62 |
| 95% CI (lower, upper) | (2,100·72, 2,670·91) | (70·02, 344·47) | (2,475·11, 3,115·90) | (83·84, 156·75) | (9·07, 11·85) |
| P-value vs. Placebo | <0·0001 | <0·0001 | <0·0001 | <0·0001 | |
| P-value vs. 10µg GBP510 with AS03 | | <0·0001 | 0·0588 | | |
| P-value vs. 25µg GBP510 with AS03 | | | | <0·0001 | |
| GMFR±standard deviation | 160·95±2·15 | 14·19±2·58 | 210·65±1·85 | 7·06±2·86 | 0·85±1·67 |
| 95% CI (lower, upper) | (135·85, 190·70) | (7·21, 27·92) | (184·50, 240·50) | (5·07, 9·83) | (0·74, 0·98) |
| P-value vs. Placebo | <0·0001 | <0·0001 | <0·0001 | <0·0001 | |
| P-value vs. 10µg GBP510 with AS03 | | <0·0001 | 0·0140 | | |
| P-value vs. 25µg GBP510 with AS03 | | | | <0·0001 | |
| SCR, n (%) | 81 (100·00) | 10 (100·00) | 85 (100·00) | 27 (65·85) | 0 (0·00) |
| 95% CI (lower, upper) | (95·55, 100·00) | (69·15, 100·00) | (95·75, 100·00) | (49·41, 79·92) | (0·00, 6·72) |
| P-value vs. Placebo | <0·0001 | <0·0001 | <0·0001 | <0·0001 | |
| P-value vs. 10µg GBP510 with AS03 | | NA | NA | | |
| P-value vs. 25µg GBP510 with AS03 | | | | <0·0001 | |
| Visit 7 (4 weeks post-2nd vaccination) | | | | | |
| n | 81 | 10 | 85 | 41 | 53 |
| GMC±standard deviation (BAU/mL) | 1,628·59±2·02 | 132·64±2·76 | 2,073·65±1·61 | 119·45±2·71 | 12·51±1·71 |
| 95% CI (lower, upper) | (1,393·34, 1,903·56) | (64·23, 273·91) | (1,870·12, 2,299·33) | (87·24, 163·56) | (10·78, 14·51) |
| P-value vs. Placebo | <0·0001 | <0·0001 | <0·0001 | <0·0001 | |
| P-value vs. 10µg GBP510 with AS03 | | <0·0001 | 0·0112 | | |
| P-value vs. 25µg GBP510 with AS03 | | | | <0·0001 | |
| GMFR±standard deviation | 110·66±2·48 | 12·12±2·37 | 157·29±1·83 | 7·35±2·85 | 1·03±1·96 |
| 95% CI (lower, upper) | (90·50, 135·32) | (6·54, 22·47) | (138·08, 179·18) | (5·29, 10·23) | (0·85, 1·23) |
| P-value vs. Placebo | <0·0001 | <0·0001 | <0·0001 | <0·0001 | |
| P-value vs. 10µg GBP510 with AS03 | | <0·0001 | 0·0041 | | |
| P-value vs. 25µg GBP510 with AS03 | | | | <0·0001 | |

| | 10µg GBP510 with AS03 (N=81) | 10µg GBP510 (N=10) | 25µg GBP510 with AS03 (N=85) | 25µg GBP510 (N=41) | Placebo (N=53) |
|---|---|---|---|---|---|
| SCR, n (%) | 80 (98·77) | 10 (100·00) | 85 (100·00) | 26 (63·41) | 1 (1·89) |
| 95% CI (lower, upper) | (93·31, 99·97) | (69·15, 100·00) | (95·75, 100·00) | (46·94, 77·88) | (0·05, 10·07) |
| P-value vs. Placebo | <0·0001 | <0·0001 | <0·0001 | <0·0001 | |
| P-value vs. 10µg GBP510 with AS03 | | 1·0000 | 0·4880 | | |
| P-value vs. 25µg GBP510 with AS03 | | | | <0·0001 | |

GMC (Geometric Mean Concentration); GMFR, geometric mean fold rise; SCR, seroconversion rate; CI, confidence interval; BAU, binding antibody unit; NA, not applicable
GMFR (Geomtetric Mean Fold Rise) = GMC (each visit) / GMC (Baseline)
SCR (Seroconversion rate): Percentage of participants with ≥ 4-fold rise from baseline
CI (Confidence Interval)
%: n / (No· of subject who information was collected at each visit by group) * 100
The 95% CI for GMC/GMFR is 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 for SCR is calculated by Clopper-Pearson Methods.
P-value vs Placebo: P-value for difference of Treatment groups versus Placebo (continuous values are two sample t-test and categorical values are chi-square test or fisher's exact test.)
P-value vs GBP510 10ug with AS03: P-value for difference of each group versus GBP510 10ug with AS03 (continuous values are two sample t-test and categorical values are chi-square test or fisher's exact test.)
P-value vs GBP510 25ug with AS03: P-value for difference of each group versus GBP510 25ug with AS03 (continuous values are two sample t-test and categorical values are chi-square test or fisher's exact test.)
n = number of participants

**Table S12. Geometric mean titers and seroconversion rates of neutralising antibody to the SARS-CoV-2 (Parental D614G Strain) in adult aged 19-64 years: analysis by pseudovirus-based neutralisation assay (per-protocol set)**

| | 10µg GBP510 with AS03 (N = 81) | 10µg GBP510 (N = 10) | 25µg GBP510 with AS03 (N = 85) | 25µg GBP510 (N = 41) | Placebo (N = 53) |
|---|---|---|---|---|---|
| Geometric mean titer and seroconversion rate | | | | | |
| Baseline | | | | | |
| n | 81 | 10 | 85 | 41 | 53 |
| GMT ± standard deviation (IU/mL) | 18·22±1·30 | 21·01±1·58 | 19·68±1·45 | 18·47±1·38 | 19·41±1·54 |
| 95% CI (lower, upper) | (17·19, 19·30) | (15·16, 29·12) | (18·16, 21·32) | (16·70, 20·43) | (17·24, 21·86) |
| P-value vs. placebo | 0·3394 | 0·5992 | 0·8426 | 0·5397 | |
| P-value vs. GBP510 10µg with AS03 | | 0·3562 | 0·1229 | | |
| P-value vs. GBP510 25µg with AS03 | | | | 0·3516 | |
| Visit 4 (4 weeks post-1st vaccination) | | | | | |
| N | 81 | 10 | 85 | 41 | 53 |
| GMT± standard deviation (IU/mL) | 38·87±2·69 | 32·79±2·45 | 43·19±2·79 | 21·03±1·64 | 19·98±1·61 |
| 95% CI (lower, upper) | (31·22, 48·38) | (17·28, 62·23) | (34·62, 53·87) | (18·01, 24·57) | (17·53, 22·78) |
| P-value vs. placebo | <0·0001 | 0·1191 | <0·0001 | 0·6107 | |
| P-value vs. GBP510 10µg with AS03 | | 0·6067 | 0·5017 | | |
| P-value vs. GBP510 25µg with AS03 | | | | <0·0001 | |
| GMFR ± standard deviation | 2·13±2·75 | 1·56±2·42 | 2·19±2·95 | 1·14±1·65 | 1·03±1·96 |
| 95% CI (lower, upper) | (1·71, 2·67) | (0·83, 2·94) | (1·74, 2·77) | (0·97, 1·33) | (0·85, 1·24) |
| P-value vs. placebo | <0·0001 | 0·0939 | <0·0001 | 0·4262 | |
| P-value vs. GBP510 10µg with AS03 | | 0·3527 | 0·8626 | | |
| P-value vs. GBP510 25µg with AS03 | | | | <0·0001 | |
| SCR, n (%) | 23 (28·40) | 1 (10·00) | 25 (29·41) | 2 (4·88) | 4 (7·55) |
| 95% CI (lower, upper) | (18·93, 39·50) | (0·25, 44·50) | (20·02, 40·29) | (0·60, 16·53) | (2·09, 18·21) |
| P-value vs. placebo | 0·0033 | 1·0000 | 0·0022 | 0·6933 | |
| P-value vs. GBP510 10µg with AS03 | | 0·2810 | 0·8852 | | |
| P-value vs. GBP510 25µg with AS03 | | | | 0·0017 | |
| Visit 6 (2 weeks post-2nd vaccination) | | | | | |
| N | 81 | 10 | 85 | 41 | 53 |
| GMT ± standard deviation (IU/mL) | 1,536·69±2·43 | 83·47±4·47 | 1,622·50±2·42 | 62·04±3·22 | 19·46±1·50 |
| 95% CI (lower, upper) | (1,262·76, 1,870·03) | (28·62, 243·48) | (1,340·93, 1,963·20) | (42·88, 89·77) | (17·41, 21·76) |

| | 10µg GBP510 with AS03 (N = 81) | 10µg GBP510 (N = 10) | 25µg GBP510 with AS03 (N = 85) | 25µg GBP510 (N = 41) | Placebo (N = 53) |
|---|---|---|---|---|---|
| P-value vs. placebo | <0·0001 | 0·0132 | <0·0001 | <0·0001 | |
| P-value vs. GBP510 10µg with AS03 | | 0·0001 | 0·6933 | | |
| P-value vs. GBP510 25µg with AS03 | | | | <0·0001 | |
| | | | | | |
| GMFR ± Standard deviation | 84·36±2·54 | 3·97±4·09 | 82·46±2·61 | 3·36±3·35 | 1·00±1·68 |
| 95% CI (lower, upper) | (68·64, 103·68) | (1·45, 10·88) | (67·05, 101·41) | (2·29, 4·92) | (0·87, 1·16) |
| P-value vs. placebo | <0·0001 | 0·0129 | <0·0001 | <0·0001 | |
| P-value vs. GBP510 10µg with AS03 | | <0·0001 | 0·8767 | | |
| P-value vs. GBP510 25µg with AS03 | | | | <0·0001 | |
| | | | | | |
| SCR, n (%) | 81 (100·00) | 5 (50·00) | 85 (100·00) | 22 (53·66) | 1 (1·89) |
| 95% CI (lower, upper) | (95·55, 100·00) | (18·71, 81·29) | (95·75, 100·00) | (37·42, 69·34) | (0·05, 10·07) |
| P-value vs. placebo | <0·0001 | 0·0002 | <0·0001 | <0·0001 | |
| P-value vs. GBP510 10µg with AS03 | | <0·0001 | NA | | |
| P-value vs. GBP510 25µg with AS03 | | | | <0·0001 | |
| Visit 7 (4 weeks post-2nd vaccination) | | | | | |
| N | 81 | 10 | 85 | 41 | 53 |
| GMT ± standard deviation (IU/mL) | 916·92±2·64 | 68·52±3·85 | 1,222·02±2·42 | 52·99±3·36 | 19·52±1·51 |
| 95% CI (lower, upper) | (740·07, 1,136·03) | (26·12, 179·79) | (1,009·72, 1,478·94) | (36·14, 77·69) | (17·42, 21·88) |
| P-value vs. placebo | <0·0001 | 0·0165 | <0·0001 | <0·0001 | |
| P-value vs. GBP510 10µg with AS03 | | <0·0001 | 0·0476 | | |
| P-value vs. GBP510 25µg with AS03 | | | | <0·0001 | |
| | | | | | |
| GMFR ± Standard deviation | 50·34±2·71 | 3·26±4·15 | 62·10±2·77 | 2·87±3·54 | 1·01±1·77 |
| 95% CI (lower, upper) | (40·39, 62·73) | (1·18, 9·02) | (49·86, 77·36) | (1·93, 4·27) | (0·86, 1·18) |
| P-value vs. placebo | <0·0001 | 0·0285 | <0·0001 | <0·0001 | |
| P-value vs. GBP510 10µg with AS03 | | <0·0001 | 0·1811 | | |
| P-value vs· GBP510 25µg with AS03 | | | | <0·0001 | |
| | | | | | |
| SCR, n (%) | 79 (97·53) | 5 (50·00) | 85 (100·00) | 18 (43·90) | 2 (3·77) |
| 95% CI (lower, upper) | (91·36, 99·70) | (18·71, 81·29) | (95·75, 100·00) | (28·47, 60·25) | (0·46, 12·98) |
| P-value vs. placebo | <0·0001 | 0·0006 | <0·0001 | <0·0001 | |
| P-value vs. GBP510 10µg with AS03 | | 0·0001 | 0·2366 | | |
| P-value vs. GBP510 25µg with AS03 | | | | <0·0001 | |

GMT, geometric mean titer; GMFR, geometric mean fold rise; SCR, seroconversion rate; CI, confidence interval

GMFR = GMT (each visit) / GMT (Baseline)

SCR: Percentage of participants with ≥ 4-fold rise from baseline

%: n / (No· of participant who information was collected at each visit by group) * 100

The 95% CI for GMT/GMFR is 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 for SCR is calculated by Clopper-Pearson Methods.

P-value versus placebo: p-value for difference of Treatment groups versus Placebo (continuous values are two sample t-test and categorical values are chi-square test or fisher's exact test)

P-value versus GBP510 10µg with AS03: p-value for difference of each group versus GBP510 10µg with AS03 (continuous values are two sample t-test and categorical values are chi-square test or fisher's exact test)

P-value versus GBP510 25µg with AS03: p-value for difference of each group versus GBP510 25µg with AS03 (continuous values are two sample t-test and categorical values are chi-square test or fisher's exact test)

Strain used in PBNA: SARS-CoV-2/Wuhan-Hu-1/surface glycoprotein/ID: NC_045512.2

**Table S13. Geometric mean concentration and seroconversion rate of IgG antibody to the SARS-CoV-2-RBD (Parental D614G Strain) in adults aged ≥65 years: analysis by enzyme-linked immunosorbent assay (per-protocol set)**

| | 10µg GBP510 with AS03 (N=12) | 10µg GBP510 (N=0) | 25µg GBP510 with AS03 (N=11) | 25µg GBP510 (N=4) | Placebo (N=5) |
|---|---|---|---|---|---|
| Geometric mean titer and seroconversion rate | | | | | |
| Baseline | | | | | |
| n | 12 | 0 | 11 | 4 | 5 |
| GMC±standard deviation (BAU/mL) | 17·78±1·45 | | 20·33±1·86 | 17·42±1·11 | 16·24±1·71 |
| 95% CI (lower, upper) | (14·02, 22·55) | | (13·39, 30·86) | (14·69, 20·67) | (8·34, 31·61) |
| P-value vs. Placebo | 0·6933 | | 0·4977 | 0·7875 | |
| P-value vs. 10µg GBP510 with AS03 | | | 0·5337 | | |
| P-value vs. 25µg GBP510 with AS03 | | | | 0·4449 | |
| Visit 4 (4 weeks post-1st vaccination) | | | | | |
| N | 12 | 0 | 11 | 4 | 5 |
| GMC±standard deviation (BAU/mL) | 64·57±2·74 | | 86·36±2·38 | 20·05±1·56 | 13·24±1·80 |
| 95% CI (lower, upper) | (34·03, 122·49) | | (48·22, 154·67) | (9·89, 40·65) | (6·39, 27·44) |
| P-value vs. Placebo | 0·0053 | | 0·0007 | 0·2815 | |
| P-value vs. 10µg GBP510 with AS03 | | | 0·4684 | | |
| P-value vs. 25µg GBP510 with AS03 | | | | 0·0075 | |
| GMFR±standard deviation | 3·63±2·79 | | 4·25±2·30 | 1·15±1·64 | 0·82±2·30 |
| 95% CI (lower, upper) | (1·89, 6·98) | | (2·43, 7·44) | (0·52, 2·53) | (0·29, 2·30) |
| P-value vs. Placebo | 0·0118 | | 0·0025 | 0·4918 | |
| P-value vs. 10µg GBP510 with AS03 | | | 0·6933 | | |
| P-value vs. 25µg GBP510 with AS03 | | | | 0·0122 | |
| SCR, n (%) | 5 (41·67) | 0 (-) | 4 (36·36) | 0 (0·00) | 0 (0·00) |
| 95% CI (lower, upper) | (15·17, 72·33) | | (10·93, 69·21) | (0·00, 60·24) | (0·00, 52·18) |
| P-value vs. Placebo | 0·2445 | | 0·2445 | NA | |
| P-value vs. 10µg GBP510 with AS03 | | | 1·0000 | | |
| P-value vs 25µg GBP510 with AS03 | | | | 0·5165 f | |

| | 10µg GBP510 with AS03 (N=12) | 10µg GBP510 (N=0) | 25µg GBP510 with AS03 (N=11) | 25µg GBP510 (N=4) | Placebo (N=5) |
|---|---|---|---|---|---|
| Visit 6 (2 weeks post-2nd vaccination) | | | | | |
| n | 12 | 0 | 11 | 4 | 5 |
| GMC±standard deviation (BAU/mL) | 1,173·91±2·40 | | 1,558·54±2·62 | 91·89±3·93 | 12·82±1·79 |
| 95% CI (lower, upper) | (673·04, 2,047·53) | | (815·94, 2,976·98) | (10·39, 812·45) | (6·21, 26·45) |
| P-value vs. Placebo | <0·0001 | | <0·0001 | 0·0218 | |
| P-value vs. 10µg GBP510 with AS03 | | | 0·4679 | | |
| P-value vs. 25µg GBP510 with AS03 | | | | 0·0006 | |
| GMFR±standard deviation | 66·03±2·69 | | 76·67±2·70 | 5·27±4·24 | 0·79±1·63 |
| 95% CI (lower, upper) | (35·20, 123·86) | | (39·34, 149·41) | (0·53, 52·50) | (0·43, 1·45) |
| P-value vs. Placebo | <0·0001 | | <0·0001 | 0·0269 | |
| P-value vs. 10µg GBP510 with AS03 | | | 0·7217 | | |
| P-value vs. 25µg GBP510 with AS03 | | | | 0·0012 | |
| SCR, n (%) | 12 (100·00) | 0 (-) | 11 (100·00) | 2 (50·00) | 0 (0·00) |
| 95% CI (lower, upper) | (73·54, 100·00) | | (71·51, 100·00) | (6·76, 93·24) | (0·00, 52·18) |
| P-value vs. Placebo | 0·0002 | | 0·0002 | 0·1667 | |
| P-value vs. 10µg GBP510 with AS03 | | | NA | | |
| P-value vs. 25µg GBP510 with AS03 | | | | 0·0571 | |
| Visit 7 (4 weeks post-2nd vaccination) | | | | | |
| n | 12 | 0 | 11 | 4 | 5 |
| GMC±standard deviation (BAU/mL) | 943·74±2·19 | | 1,177·45±2·67 | 77·68±3·39 | 12·70±1·74 |
| 95% CI (lower, upper) | (573·91, 1,551·88) | | (608·78, 2,277·31) | (11·13, 542·43) | (6·40, 25·19) |
| P-value vs. Placebo | <0·0001 | | <0·0001 | 0·0201 | |
| P-value vs. 10µg GBP510 with AS03 | | | 0·5548 | | |
| P-value vs. 25µg GBP510 with AS03 | | | | 0·0006 | |
| GMFR±standard deviation | 53·08±2·41 | | 57·92±2·64 | 4·46±3·70 | 0·78±1·50 |
| 95% CI (lower, upper) | (30·38, 92·74) | | (30·18, 111·16) | (0·56, 35·68) | (0·47, 1·29) |
| P-value vs. Placebo | <0·0001 | | <0·0001 | 0·0717 | |
| P-value vs. 10µg GBP510 with AS03 | | | 0·8230 | | |
| P-value vs 25µg GBP510 with AS03 | | | | 0·0011 | |

| | 10µg GBP510 with AS03 (N=12) | 10µg GBP510 (N=0) | 25µg GBP510 with AS03 (N=11) | 25µg GBP510 (N=4) | Placebo (N=5) |
|---|---|---|---|---|---|
| SCR, n (%) | 12 (100·00) | 0 (-) | 11 (100·00) | 2 (50·00) | 0 (0·00) |
| 95% CI (lower, upper) | (73·54, 100·00) | | (71·51, 100·00) | (6·76, 93·24) | (0·00, 52·18) |
| P-value vs. Placebo | 0·0002 | | 0·0002 | 0·1667 | |
| P-value vs. 10µg GBP510 with AS03 | | | NA | | |
| P-value vs. 25µg GBP510 with AS03 | | | | 0·0571 | |

GMC (Geometric Mean Concentration); GMFR, geometric mean fold rise; SCR, seroconversion rate; CI, confidence interval; BAU, binding antibody unit; NA, not applicable
GMFR (Geomtetric Mean Fold Rise) = GMC (each visit) / GMC (Baseline)
SCR (Seroconversion rate): Percentage of participants with ≥ 4-fold rise from baseline
CI (Confidence Interval)
%: n / (No. of subject who information was collected at each visit by group) * 100
The 95% CI for GMC/GMFR is 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 for SCR is calculated by Clopper-Pearson Methods.
P-value vs Placebo: P-value for difference of Treatment groups versus Placebo (continuous values are two sample t-test and categorical values are chi-square test or fisher's exact test.)
P-value vs GBP510 10ug with AS03: P-value for difference of each group versus GBP510 10ug with AS03 (continuous values are two sample t-test and categorical values are chi-square test or fisher's exact test.)
P-value vs GBP510 25ug with AS03: P-value for difference of each group versus GBP510 25ug with AS03 (continuous values are two sample t-test and categorical values are chi-square test or fisher's exact test.)
n = number of participants

**Table S14. Geometric mean titers and seroconversion rates of neutralising antibody to the SARS-CoV-2 (Parental D614G Strain) in adult aged ≥65 years: analysis by pseudovirus-based neutralisation assay (per-protocol set)**

| | 10µg GBP510 with AS03 (N = 12) | 10µg GBP510 (N = 0) | 25µg GBP510 with AS03 (N = 11) | 25µg GBP510 (N = 4) | Placebo (N = 5) |
|---|---|---|---|---|---|
| Geometric mean titer and seroconversion rate | | | | | |
| Baseline | | | | | |
| n | 12 | 0 | 11 | 4 | 5 |
| GMT ± standard deviation (IU/mL) | 17·00±1·00 | | 18·11±1·23 | 26·14±2·36 | 17·00±1·00 |
| 95% CI (lower, upper) | (17·00, 17·00) | | (15·73, 20·83) | (6·65, 102·76) | (17·00, 17·00) |
| P-value vs. placebo | NA | | 0·3409 | 0·3910 t | |
| P-value vs. GBP510 10µg with AS03 | | | 0·3409 | | |
| P-value vs. GBP510 25µg with AS03 | | | | 0·4581 | |
| Visit 4 (4 weeks post-1st vaccination) | | | | | |
| n | 12 | 0 | 11 | 4 | 5 |
| GMT± standard deviation (IU/mL) | 48·31±3·04 | | 27·12±2·47 | 23·30±1·88 | 17·00±1·00 |
| 95% CI (lower, upper) | (23·82, 97·97) | | (14·76, 49·81) | (8·54, 63·55) | (17·00, 17·00) |
| P-value vs. placebo | 0·0077 | | 0·1178 | 0·3910 | |
| P-value vs. GBP510 10µg with AS03 | | | 0·1891 | | |
| P-value vs. GBP510 25µg with AS03 | | | | 0·7646 | |
| GMFR ± standard deviation | 2·84±3·04 | | 1·50±2·62 | 0·89±1·26 | 1·00±1·00 |
| 95% CI (lower, upper) | (1·40, 5·76) | | (0·78, 2·86) | (0·62, 1·28) | (1·00, 1·00) |
| P-value vs. placebo | 0·0077 | | 0·1944 | 0·3910 t | |
| P-value vs. GBP510 10µg with AS03 | | | 0·1566 | | |
| P-value vs. GBP510 25µg with AS03 | | | | 0·1218 t | |
| SCR, n (%) | 5 (41·67) | 0 (-) | 2 (18·18) | 0 (0·00) | 0 (0·00) |
| 95% CI (lower, upper) | (15·17, 72·33) | | (2·28, 51·78) | (0·00, 60·24) | (0·00, 52·18) |
| P-value vs. placebo | 0·2445 | | 1·0000 | NA | |
| P-value vs. GBP510 10µg with AS03 | | | 0·3707 | | |
| P-value vs. GBP510 25µg with AS03 | | | | 1·0000 | |
| Visit 6 (2 weeks post-2nd vaccination) | | | | | |
| n | 12 | 0 | 11 | 4 | 5 |
| GMT ± standard deviation (IU/mL) | 627·68±2·91 | | 543·68±3·55 | 85·71±5·08 | 17·00±1·00 |
| 95% CI (lower, upper) | (318·55, 1,236·78) | | (232·19, 1,273·06) | (6·45, 1,138·93) | (17·00, 17·00) |

| | 10µg GBP510 with AS03 (N = 12) | 10µg GBP510 (N = 0) | 25µg GBP510 with AS03 (N = 11) | 25µg GBP510 (N = 4) | Placebo (N = 5) |
|---|---|---|---|---|---|
| P-value vs. placebo | <0·0001 | | <0·0001 | 0·1406 | |
| P-value vs. GBP510 10µg with AS03 | | | 0·7709 | | |
| P-value vs· GBP510 25µg with AS03 | | | | 0·0365 | |
| | | | | | |
| GMFR ± Standard deviation | 36·92±2·91 | | 30·03±3·93 | 3·28±5·56 | 1·00±1·00 |
| 95% CI (lower, upper) | (18·74, 72·75) | | (11·97, 75·33) | (0·21, 50·23) | (1·00, 1·00) |
| P-value vs. placebo | <0·0001 | | <0·0001 t | 0·2601 | |
| P-value vs. GBP510 10µg with AS03 | | | 0·6891 t | | |
| P-value vs. GBP510 25µg with AS03 | | | | 0·0218 | |
| | | | | | |
| SCR, n (%) | 12 (100·00) | 0 (-) | 10 (90·91) | 1 (25·00) | 0 (0·00) |
| 95% CI (lower, upper) | (73·54, 100·00) | | (58·72, 99·77) | (0·63, 80·59) | (0·00, 52·18) |
| P-value vs. placebo | 0·0002 | | 0·0014 | 0·4444 | |
| P-value vs. GBP510 10µg with AS03 | | | 0·4783 | | |
| P-value vs. GBP510 25µg with AS03 | | | | 0·0330 | |
| Visit 7 (4 weeks post-2nd vaccination) | | | | | |
| n | 12 | 0 | 11 | 4 | 5 |
| GMT ± standard deviation (IU/mL) | 459·81±2·99 | | 517·02±3·37 | 41·70±3·88 | 17·00±1·00 |
| 95% CI (lower, upper) | (229·26, 922·22) | | (228·65, 1,169·08) | (4·82, 361·16) | (17·00, 17·00) |
| P-value vs. placebo | <0·0001 | | <0·0001 | 0·2777 | |
| P-value vs. GBP510 10µg with AS03 | | | 0·8100 | | |
| P-value vs. GBP510 25µg with AS03 | | | | 0·0043 | |
| | | | | | |
| GMFR ± Standard deviation | 27·05±2·99 | | 28·56±3·83 | 1·60±6·69 | 1·00±1·00 |
| 95% CI (lower, upper) | (13·49, 54·25) | | (11·58, 70·40) | (0·08, 32·80) | (1·00, 1·00) |
| P-value vs. placebo | <0·0001 | | <0·0001 | 0·6566 | |
| P-value vs. GBP510 10µg with AS03 | | | 0·9161 | | |
| P-value vs. GBP510 25µg with AS03 | | | | 0·0056 | |
| | | | | | |
| SCR, n (%) | 12 (100·00) | 0 (-) | 10 (90·91) | 1 (25·00) | 0 (0·00) |
| 95% CI (lower, upper) | (73·54, 100·00) | | (58·72, 99·77) | (0·63, 80·59) | (0·00, 52·18) |
| P-value vs. placebo | 0·0002 | | 0·0014 | 0·4444 | |
| P-value vs. GBP510 10µg with AS03 | | | 0·4783 | | |
| P-value vs. GBP510 25µg with AS03 | | | | 0·0330 | |

GMT, geometric mean titer; GMFR, geometric mean fold rise; SCR, seroconversion rate; CI, confidence interval

GMFR = GMT (each visit) / GMT (Baseline)

SCR: Percentage of participants with ≥ 4-fold rise from baseline

%: n / (No· of participant who information was collected at each visit by group) * 100

The 95% CI for GMT/GMFR is 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 for SCR is calculated by Clopper-Pearson Methods.

P-value versus placebo: p-value for difference of Treatment groups versus Placebo (continuous values are two sample t-test and categorical values are chi-square test or fisher's exact test)

P-value versus GBP510 10µg with AS03: p-value for difference of each group versus GBP510 10µg with AS03 (continuous values are two sample t-test and categorical values are chi-square test or fisher's exact test)

P-value versus GBP510 25µg with AS03: p-value for difference of each group versus GBP510 25µg with AS03 (continuous values are two sample t-test and categorical values are chi-square test or fisher's exact test)

Strain used in PBNA: SARS-CoV-2/Wuhan-Hu-1/surface glycoprotein/ID: NC_045512.2

**Table S15. Cell-mediated response for CD4+ T cells expressing cytokines using intracellular cytokine staining (per-protocol set)**

| | 10µg GBP510 with AS03 (N=93) | 10µg GBP510 (N=10) | 25µg GBP510 with AS03 (N=96) | 25µg GBP510 (N=45) | Placebo (N=58) |
|---|---|---|---|---|---|
| IFN-γ | | | | | |
| Baseline (day 0) | | | | | |
| n | 19 | 2 | 17 | 7 | 15 |
| Median | 0.00 | 0.01 | 0.01 | 0.01 | 0.00 |
| IQR (Q1, Q3) | (0.00, 0.04) | (0.00, 0.01) | (0.00, 0.02) | (0.00, 0.03) | (0.00, 0.01) |
| Visit 4 (day 28) | | | | | |
| n | 19 | 2 | 17 | 7 | 15 |
| Median | 0.01 | 0.01 | 0.03 | 0.01 | 0.01 |
| IQR (Q1, Q3) | (0.00, 0.04) | (0.00, 0.01) | (0.01, 0.06) | (0.00, 0.07) | (0.00, 0.03) |
| Visit 6 (day 42) | | | | | |
| n | 19 | 2 | 17 | 7 | 15 |
| Median | 0.06 | 0.00 | 0.06 | 0.02 | 0.02 |
| IQR (Q1, Q3) | (0.02, 0.11) | (0.00, 0.01) | (0.01, 0.12) | (0.01, 0.04) | (0.00, 0.04) |
| TNFα | | | | | |
| Baseline (day 0) | | | | | |
| n | 19 | 2 | 17 | 7 | 15 |
| Median | 0.06 | 0.06 | 0.05 | 0.03 | 0.02 |
| IQR (Q1, Q3) | (0.02, 0.20) | (0.04, 0.09) | (0.03, 0.08) | (0.00, 0.07) | (0.01, 0.06) |
| Visit 4 (day 28) | | | | | |
| n | 19 | 2 | 17 | 7 | 15 |
| Median | 0.13 | 0.03 | 0.09 | 0.13 | 0.09 |
| IQR (Q1, Q3) | (0.06, 0.30) | (0.00, 0.06) | (0.03, 0.35) | (0.06, 0.32) | (0.04, 0.26) |
| Visit 6 (day 42) | | | | | |
| n | 19 | 2 | 17 | 7 | 15 |
| Median | 0.24 | 0.18 | 0.27 | 0.25 | 0.12 |
| IQR (Q1, Q3) | (0.19, 0.59) | (0.02, 0.34) | (0.10, 0.52) | (0.04, 0.32) | (0.05, 0.49) |
| IL-2 | | | | | |
| Baseline (day 0) | | | | | |
| n | 19 | 2 | 17 | 7 | 15 |

| | 10µg GBP510 with AS03 (N=93) | 10µg GBP510 (N=10) | 25µg GBP510 with AS03 (N=96) | 25µg GBP510 (N=45) | Placebo (N=58) |
|---|---|---|---|---|---|
| Median | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 |
| IQR (Q1, Q3) | (0.01, 0.03) | (0.01, 0.01) | (0.00, 0.02) | (0.00, 0.02) | (0.00, 0.02) |
| Visit 4 (day 28) | | | | | |
| n | 19 | 2 | 17 | 7 | 15 |
| Median | 0.03 | 0.02 | 0.03 | 0.02 | 0.02 |
| IQR (Q1, Q3) | (0.01, 0.04) | (0.00, 0.03) | (0.01, 0.05) | (0.00, 0.04) | (0.00, 0.04) |
| Visit 6 (day 42) | | | | | |
| n | 19 | 2 | 17 | 7 | 15 |
| Median | 0.11 | 0.02 | 0.10 | 0.04 | 0.01 |
| IQR (Q1, Q3) | (0.07, 0.13) | (0.01, 0.03) | (0.04, 0.15) | (0.01, 0.04) | (0.00, 0.06) |
| IL-4 | | | | | |
| Baseline (day 0) | | | | | |
| n | 19 | 2 | 17 | 7 | 15 |
| Median | 0.01 | 0.04 | 0.01 | 0.00 | 0.02 |
| IQR (Q1, Q3) | (0.00, 0.03) | (0.00, 0.08) | (0.00, 0.10) | (0.00, 0.04) | (0.00, 0.04) |
| Visit 4 (day 28) | | | | | |
| n | 19 | 2 | 17 | 7 | 15 |
| Median | 0.00 | 0.00 | 0.02 | 0.02 | 0.01 |
| IQR (Q1, Q3) | (0.00, 0.02) | (0.00, 0.00) | (0.01, 0.04) | (0.00, 0.10) | (0.00, 0.12) |
| Visit 6 (day 42) | | | | | |
| n | 19 | 2 | 17 | 7 | 15 |
| Median | 0.00 | 0.00 | 0.00 | 0.00 | 0.01 |
| IQR (Q1, Q3) | (0.00, 0.06) | (0.00, 0.00) | (0.00, 0.05) | (0.00, 0.04) | (0.00, 0.04) |
| IL-5 | | | | | |
| Baseline (day 0) | | | | | |
| n | 19 | 2 | 17 | 7 | 15 |
| Median | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| IQR (Q1, Q3) | (0.00, 0.01) | (0.00, 0.00) | (0.00, 0.00) | (0.00, 0.00) | (0.00, 0.00) |
| Visit 4 (day 28) | | | | | |
| n | 19 | 2 | 17 | 7 | 15 |
| Median | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| IQR (Q1, Q3) | (0.00, 0.00) | (0.00, 0.00) | (0.00, 0.01) | (0.00, 0.01) | (0.00, 0.01) |

| | 10µg GBP510 with AS03 (N=93) | 10µg GBP510 (N=10) | 25µg GBP510 with AS03 (N=96) | 25µg GBP510 (N=45) | Placebo (N=58) |
|---|---|---|---|---|---|
| Visit 6 (day 42) | | | | | |
| n | 19 | 2 | 17 | 7 | 15 |
| Median | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| IQR (Q1, Q3) | (0.00, 0.00) | (0.00, 0.00) | (0.00, 0.01) | (0.00, 0.01) | (0.00, 0.01) |

N= Total number of participants in each vaccine group; n = number of participants in each visit; IQR=Interquartile range; Q1=Quartile 3; Q1=Quartile 3.
RBD-specific CD4+ T cells producing the indicated cytokine as a fraction of total cytokine-producing RBD-specific CD4+ T cells.

**Figure S1. Clinical trial scheme.**

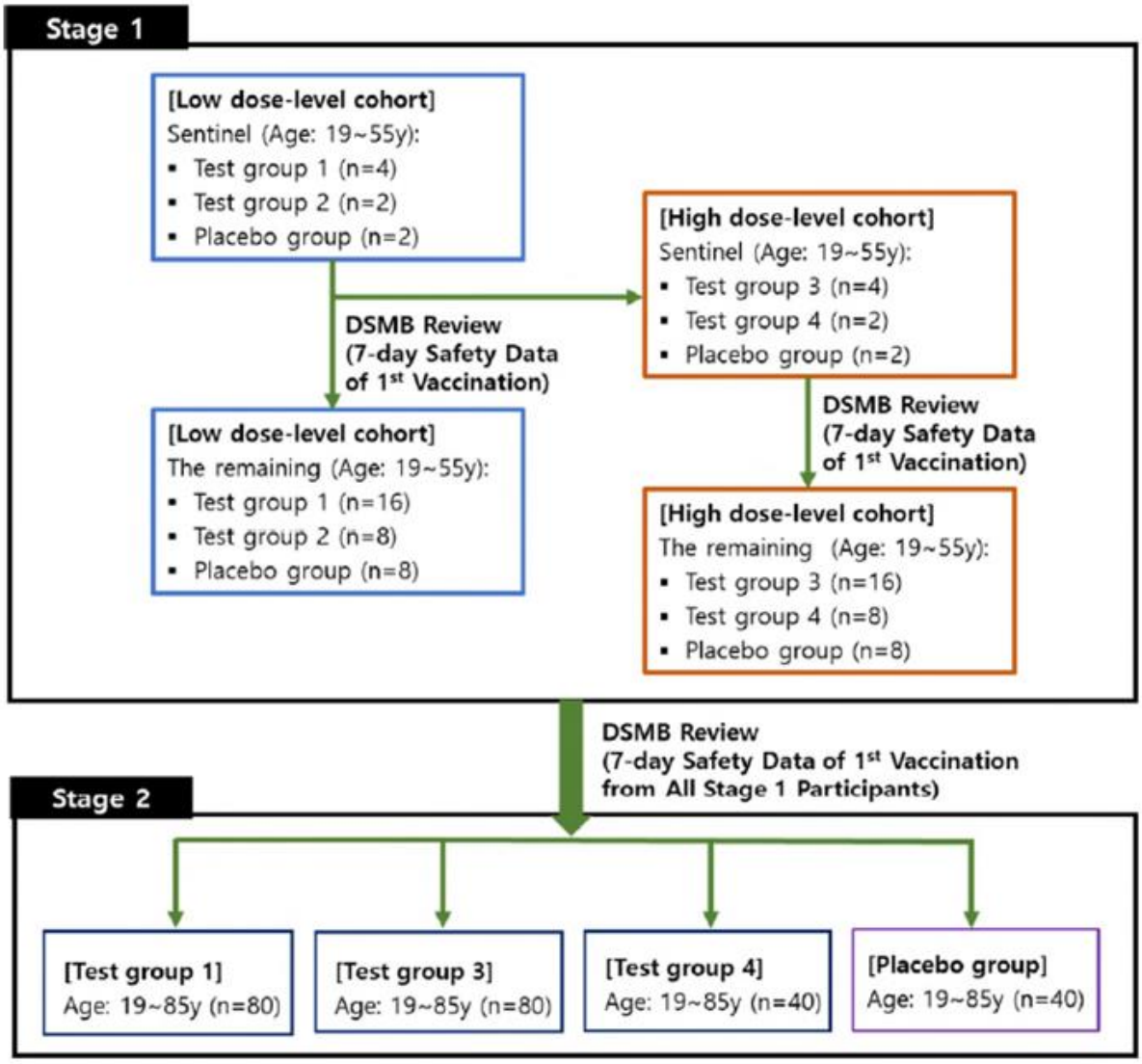
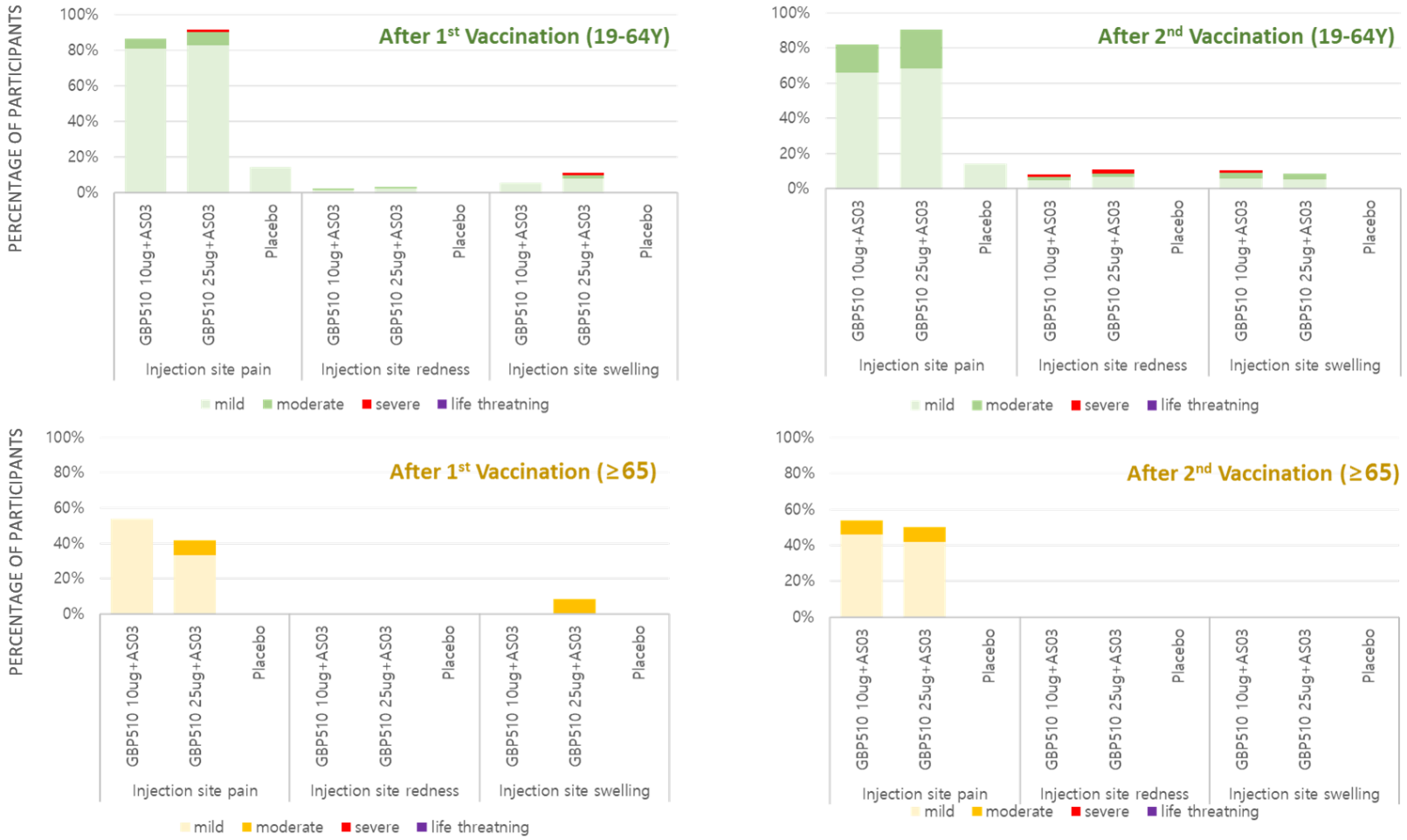


**Figure S2. Vaccine trial groups and timeline.**

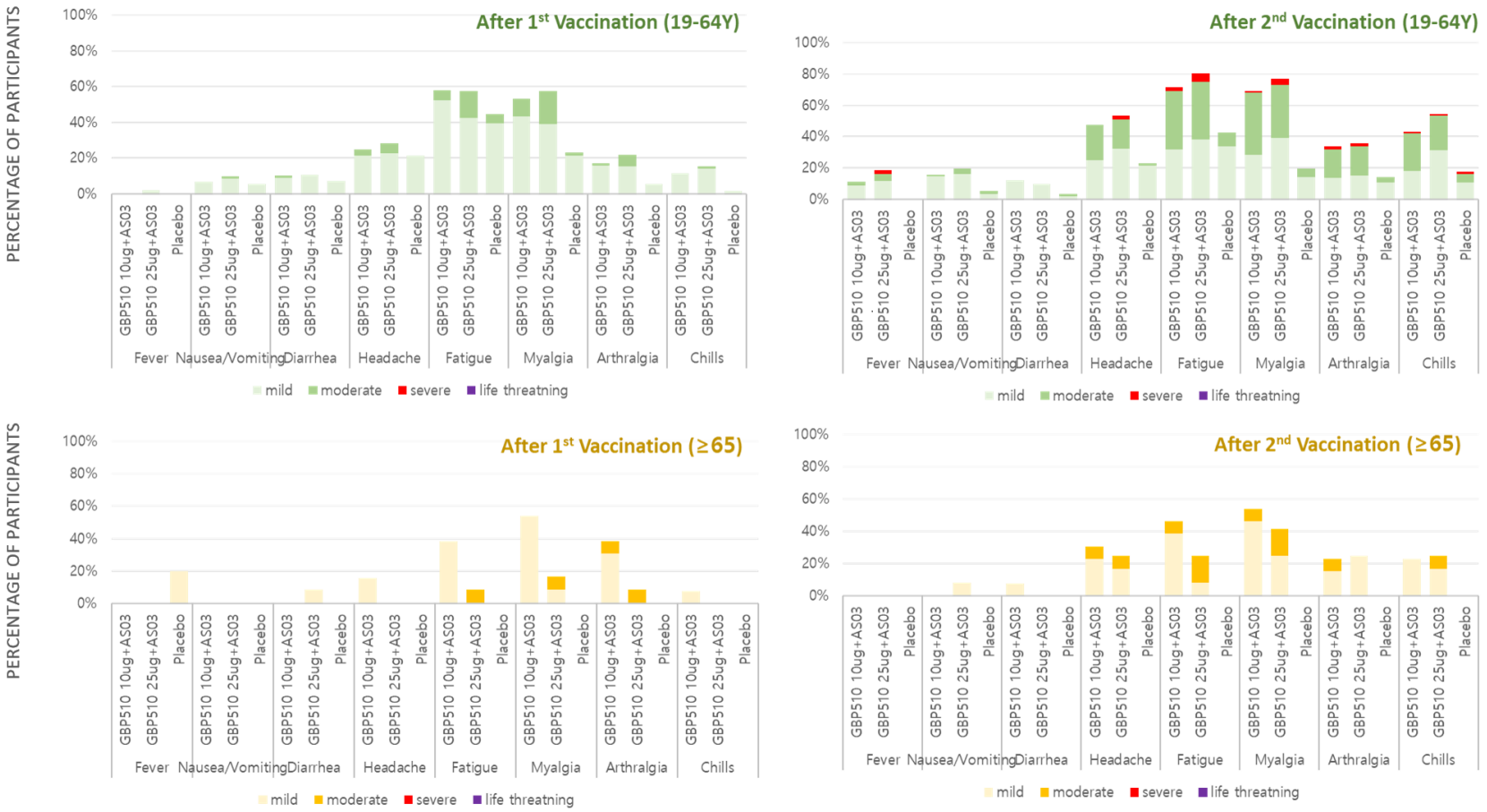
| | Group 1 | Group 2 | Group 3 | Group 4 | | |
|---|---|---|---|---|---|---|
| | GBP510 10 µg with AS03 | GBP510 10 µg | GBP510 25 µg with AS03 | GBP510 25 µg | Placebo | Total |
| Screened | - | | - | - | - | 353 |
| Randomization | 101 | 10 | 104 | 52 | 61 | 328 |
| Intention-to-treat set | 101 | 10 | 104 | 52 | 61 | 328 |
| Safety set | 101 | 10 | 104 | 51 | 61 | 327 |
| Per-protocol set | 93 | 10 | 96 | 45 | 58 | 302 |

| | Screening (visit 1) | Day 0 (visit 2) | Day 7 (visit 3) | Day 28 (visit 4) | Day 35 (visit 5) | Day 42 (visit 6) | Day 56 (visit 7) | Day 84 (visit 8) | Day 168 (visit 9) | Day 365 (visit 10) |
|---|---|---|---|---|---|---|---|---|---|---|
| Vaccination | | x | | x | | | | | | |
| Blood sample (safety) | x | | x | | | | x | | | |
| Blood sample (immunogenicity) | | x | | x | | x | x | x | x | x |
| Solicited AE | | ← | → | ← | → | | | | | |
| Unsolicited AE | | ← | | | | | → | | | |
| SAE, MAAE, AESI | | ← | | | | | | | | → |

**Figure S3. Age-stratified analysis of solicited local (A) and systemic (B) adverse events within 7 days after first-dose and second-dose (proportion of participants with adverse events).**



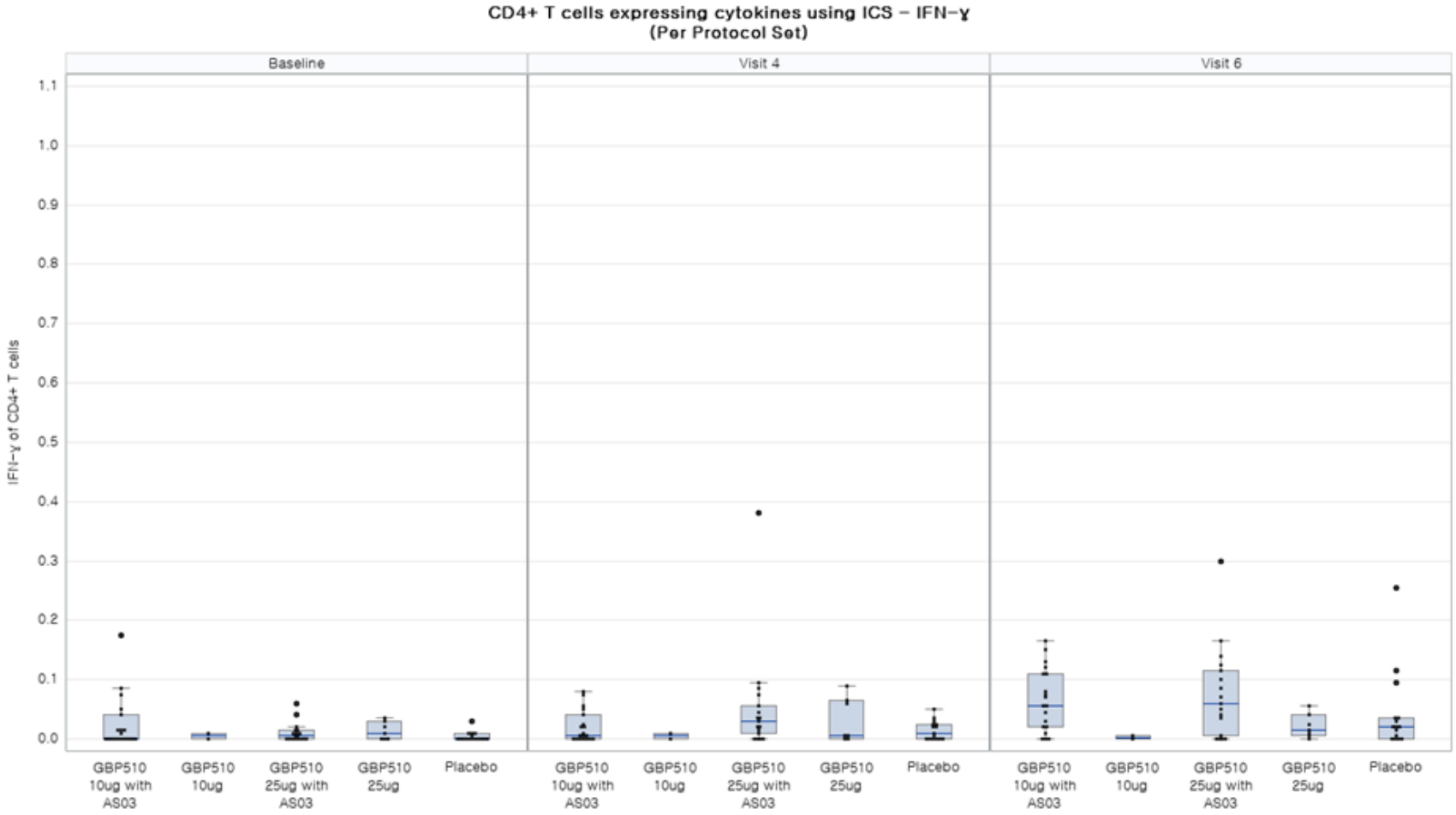

**(A)**


After 1st Vaccination (19-64Y)
After 2nd Vaccination (19-64Y)
After 1st Vaccination (≥65)
After 2nd Vaccination (≥65)
PERCENTAGE OF PARTICIPANTS
100%
80%
60%
40%
20%
0%
GBP510 10ug+AS03
GBP510 25ug+AS03
Placebo
Fever
Nausea/Vomiting
Diarrhea
Headache
Fatigue
Myalgia
Arthralgia
Chills
mild
moderate
severe
life threatning

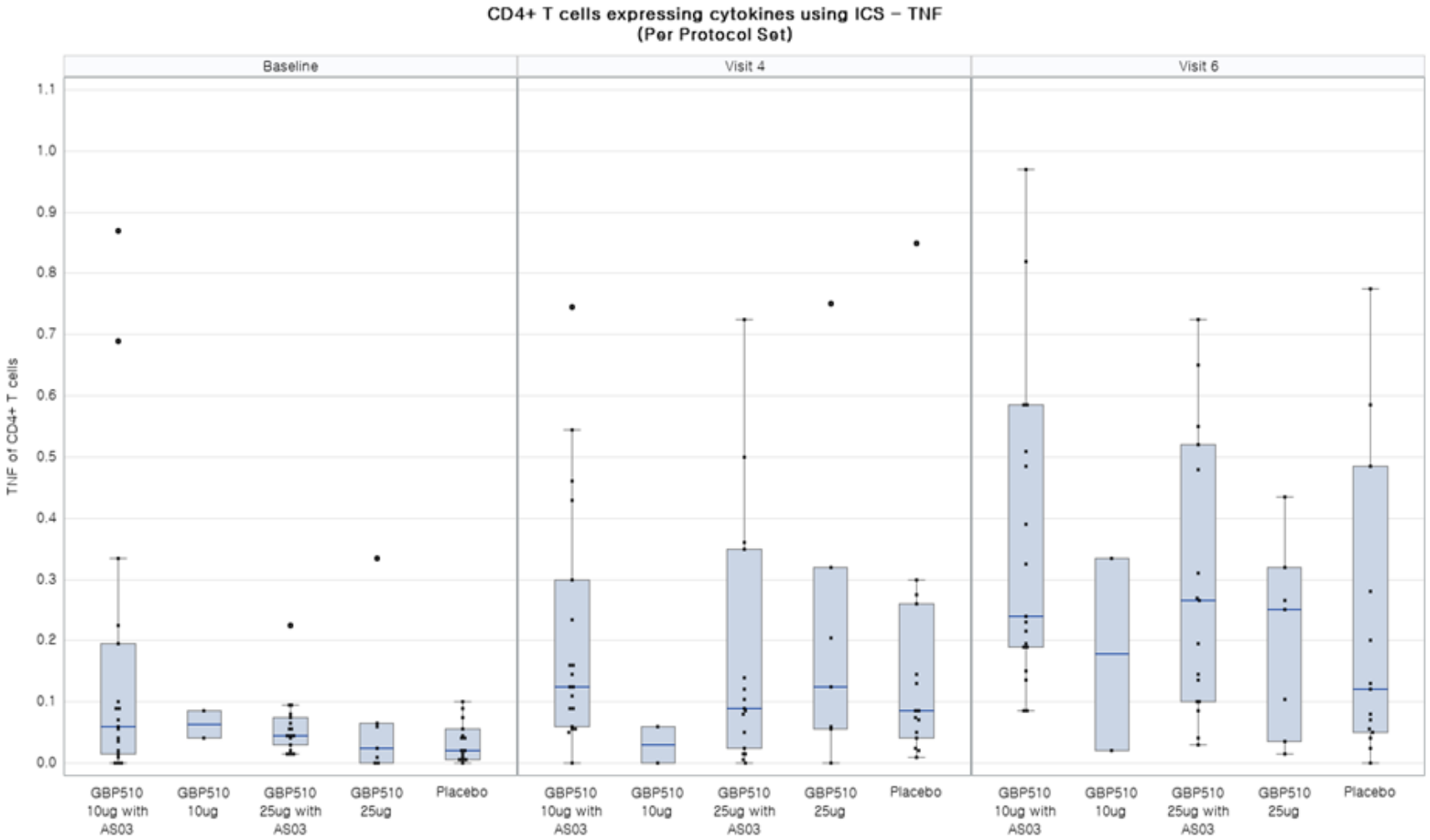
**(B)**

**Figure S4. Boxplot for the IFN-γ (A), TNF-α (B), IL-2 (C), IL-4 (D), IL-5 (E) of cell-mediated immune responses for CD4+ T-cells expressing cytokines using intracellular cytokine staining at baseline (day 0), visit 4 (day 28) and visit 6 (day 42).**

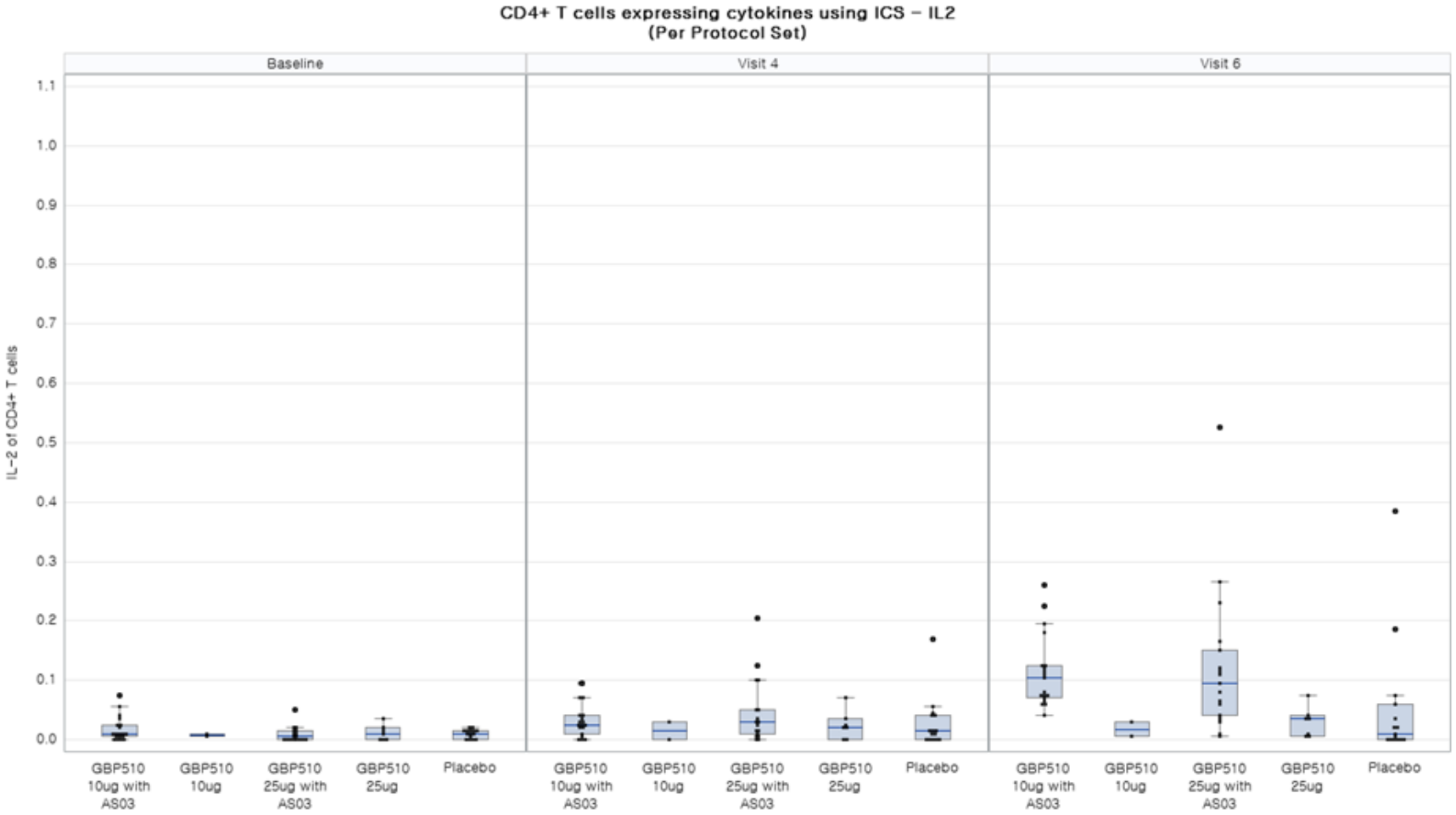
**(A)**



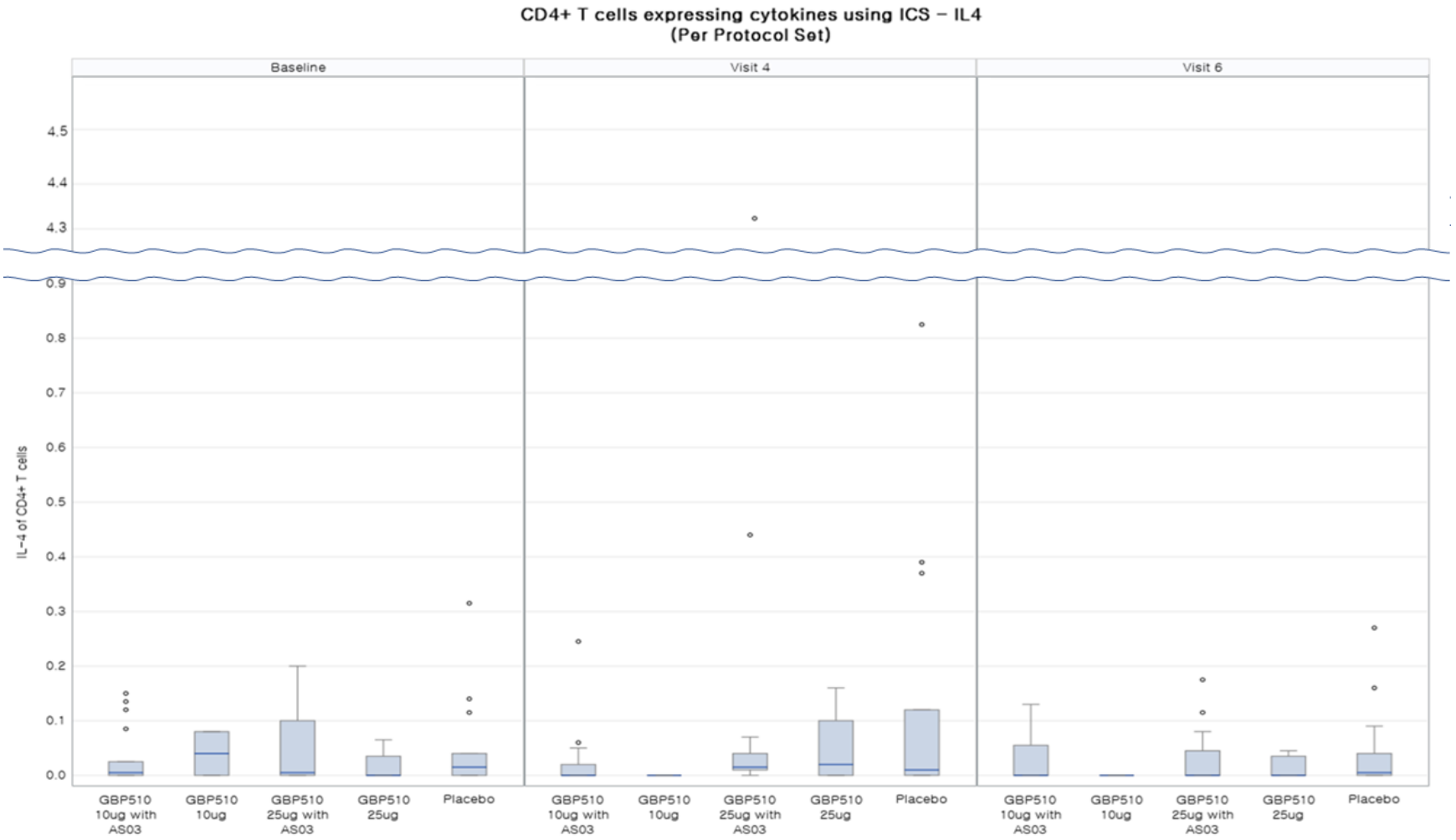
**(B)**


CD4+ T cells expressing cytokines using ICS – TNF
(Per Protocol Set)
Baseline
Visit 4
Visit 6
TNF of CD4+ T cells
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
GBP510 10ug with AS03
GBP510 10ug
GBP510 25ug with AS03
GBP510 25ug
Placebo

**(C)**


CD4+ T cells expressing cytokines using ICS – IL2
(Per Protocol Set)
Baseline
Visit 4
Visit 6
IL-2 of CD4+ T cells
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
GBP510 10ug with AS03
GBP510 10ug
GBP510 25ug with AS03
GBP510 25ug
Placebo

**(D)**


CD4+ T cells expressing cytokines using ICS – IL4
(Per Protocol Set)
Baseline
Visit 4
Visit 6
IL-4 of CD4+ T cells
4.5
4.4
4.3
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
GBP510 10ug with AS03
GBP510 10ug
GBP510 25ug with AS03
GBP510 25ug
Placebo

**(E)**

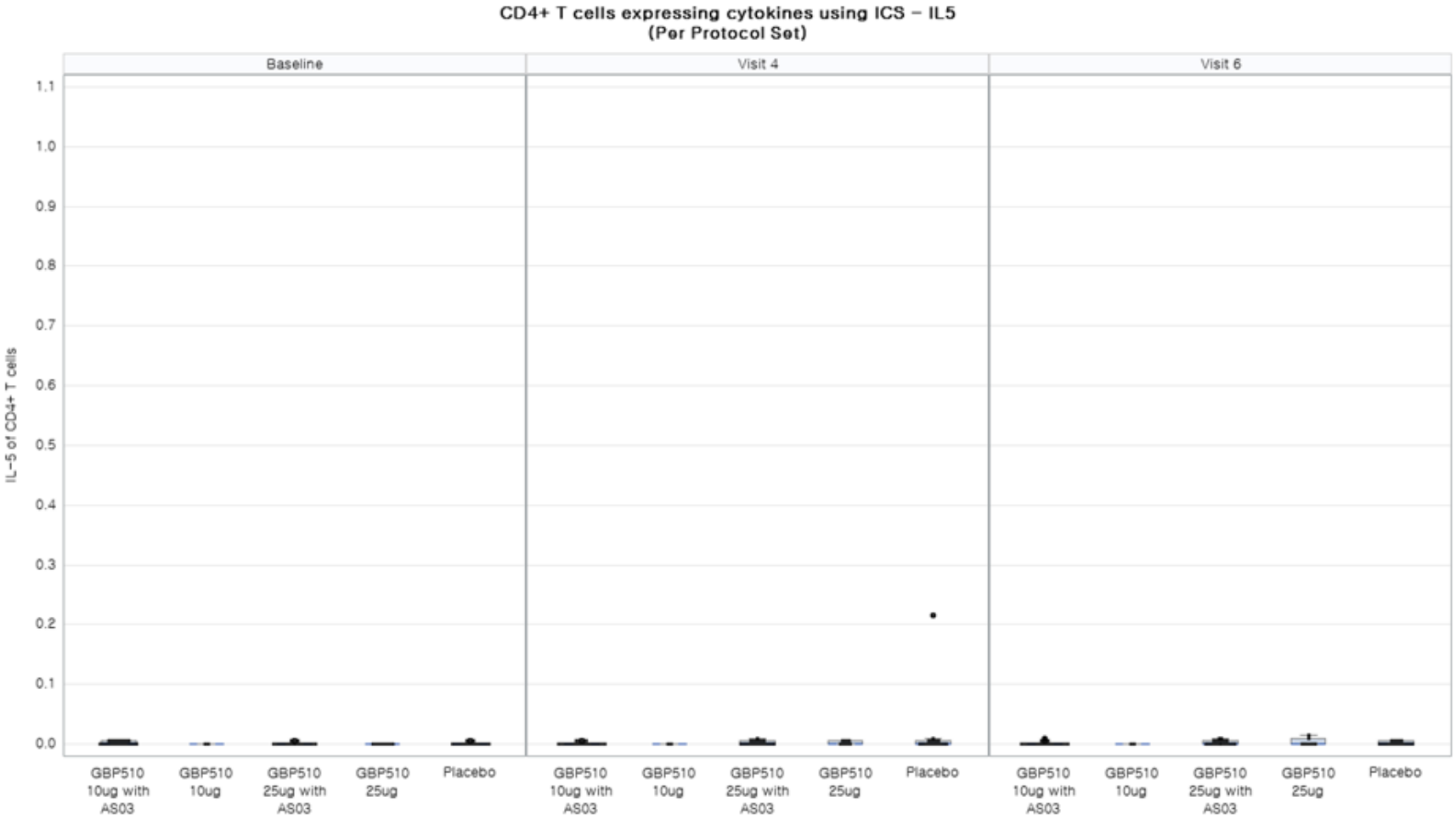
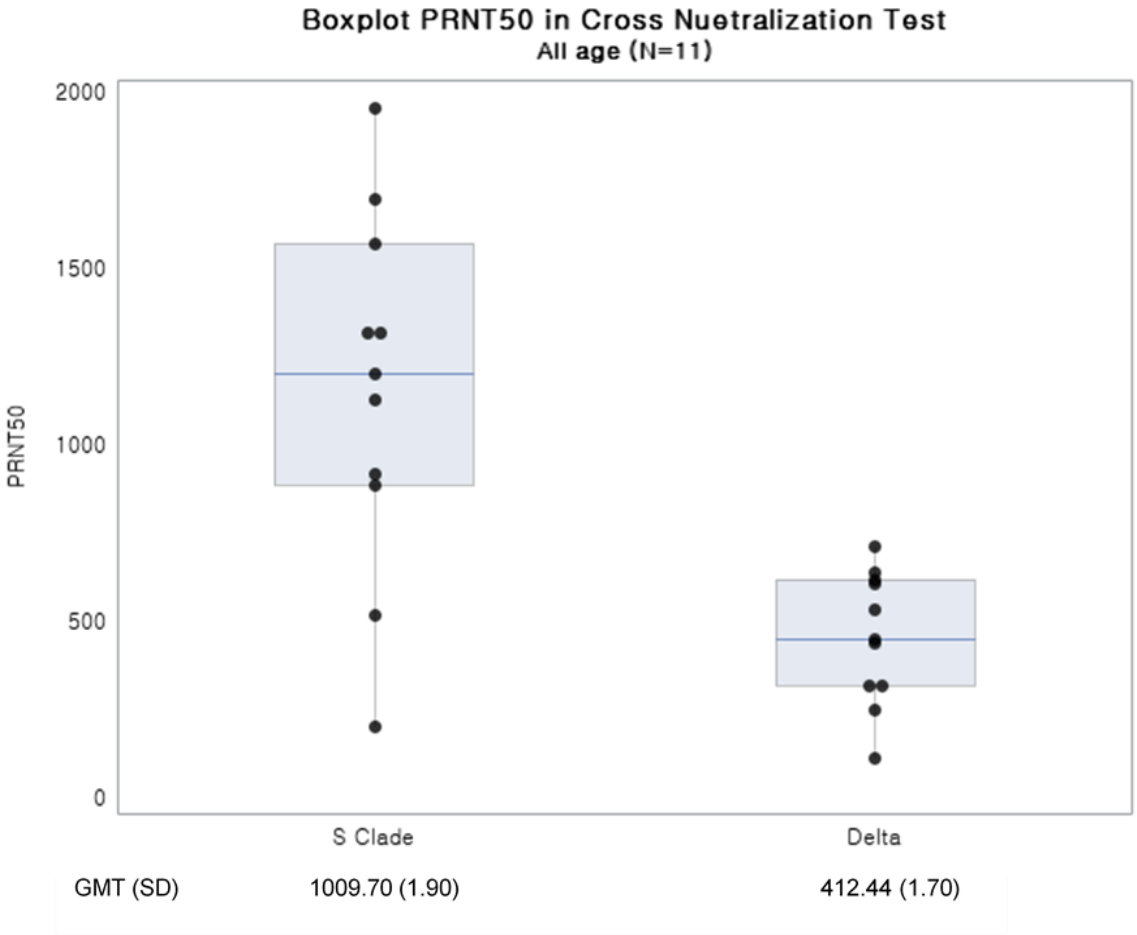
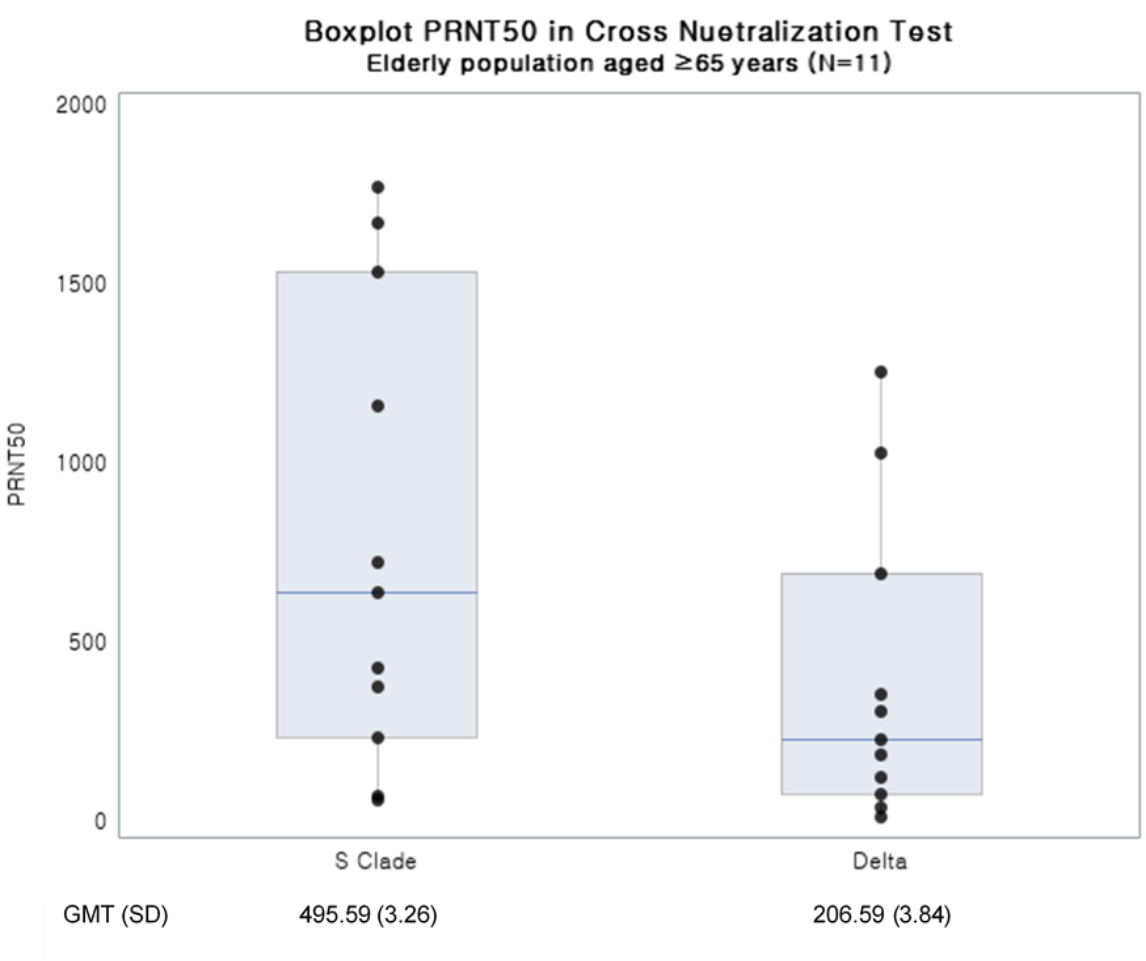

CD4+ T cells expressing cytokines using ICS – IL5
(Per Protocol Set)
Baseline
Visit 4
Visit 6
IL-5 of CD4+ T cells
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
GBP510 10ug with AS03
GBP510 10ug
GBP510 25ug with AS03
GBP510 25ug
Placebo

**Figure S5. Cross-reactive immunogenicity against the delta variant virus (B·1·617) in 25 µg GBP510 adjuvanted with AS03 recipients, assessed by the plaque reduction neutralisation test (PRNT). Data from randomly selected 11 participants aged 19–85 years (A). Data from randomly selected 11 participants aged ≥ 65 years.**

**(A)**



**(B)**


Boxplot PRNT50 in Cross Nuetralization Test
Elderly population aged ≥65 years (N=11)
PRNT50
2000
1500
1000
500
0
S Clade
Delta
GMT (SD)
495.59 (3.26)
206.59 (3.84)

# II. Study protocol of GBP510

# Title Page

**Protocol Title:**

A 2-Stage, Phase I/II, Placebo-controlled, Randomized, Observer-blinded, Dose-finding Study to Assess the Safety, Reactogenicity, and Immunogenicity of a SARS-CoV-2 Recombinant Protein Nanoparticle Vaccine (GBP510) adjuvanted with or without AS03 in Healthy Younger and Older Adults

**Protocol Number:** GBP510_002

**Amendment Number:** Not Applicable

**Compound:** GBP510

**Brief Title:** A Phase I/II Study to Assess the Safety, Reactogenicity, and Immunogenicity of a SARS-CoV-2 Recombinant Protein Nanoparticle Vaccine (GBP510) adjuvanted with or without AS03 in Healthy Younger and Older Adults

**Study Phase:** Phase I/II

**Study Participants:** Healthy younger and older adults aged 19 to 85 years

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

**Manufacturer:** SK bioscience Co., Ltd.

**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)**

[MFDS: 202100079]

**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 3.0<br>19 Mar 2021 | ▪ Change of safety evaluation criteria to advance from Stage 1 to Stage 2<br>▪ Allows code-breaking of participants for authorized COVID-19 vaccination.<br>▪ Deletion of stepwize approach to study vaccination for the elderly participants aged 75 years and older<br>▪ Increase in blood collection volume for humoral immunogenicity analysis |
| Version 2.0<br>18 Jan 2021 | ▪ Sample size increased (a total of 260 → 320)<br>▪ Stepwise approach to study vaccination for the elderly participants aged 75 years and older<br>▪ Study objectives and endpoints are presented by stage |
| Version 1.0<br>17 Dec 2020 | N/A |

# Table of Contents

# 1. Protocol Summary

## 1.1. Synopsis

**Protocol Title:** A 2-Stage, Phase I/II, Placebo-controlled, Randomized, Observer-blinded, Dose-finding Study to Assess the Safety, Reactogenicity, and Immunogenicity of a SARS-CoV-2 Recombinant Protein Nanoparticle Vaccine (GBP510) adjuvanted with or without AS03 in Healthy Younger and Older Adults.

**Brief Title:** A Phase I/II Study to Assess the Safety, Reactogenicity, and Immunogenicity of a SARS-CoV-2 Recombinant Protein Nanoparticle Vaccine (GBP510) adjuvanted with or without AS03 in Healthy Younger and Older Adults.

**Rationale**: Since the first report of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in Wuhan, China in December 2019, more than 65 million cases of COVID-19 including a million deaths have been reported from over 221 countries and territories around the world as of today. Thus, the development of vaccine to protect the risk populations and to reduce the burden on health care infrastructure is one of the top global health priorities. However, there are currently no vaccines approved for prevention of COVID-19, and WHO announced that 51 vaccine candidates are in the clinical trial stage as of Dec 2nd, 2020. Among several different platform technologies that are being used for the development of COVID-19 vaccines such as DNA, mRNA, recombinant protein and viral vector, 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 safety and product stability. Accordingly, SK bioscience developed a protein-based vaccine which is a self-assembling nanoparticle of receptor-binding domain (RBD) of SARS-CoV-2 spike protein adjuvanted with AS03, in collaboration with Institute for Protein Design (IPD) at University of Washington (UW) and GlaxoSmithKline

**Objectives and Endpoints**:

**For Stage 1**

| **Primary Endpoints** | |
|---|---|
| **Objectives** | **Endpoints** |
| To assess the reactogenicity and safety profile of GBP510 vaccines in healthy younger adults post each vaccination | ▪ Occurrence of immediate systemic reactions<br>▪ Occurrence of solicited local AEs during 7 days post each vaccination<br>▪ Occurrence of solicited systemic AEs during 7 days post each vaccination<br>▪ Occurrence of unsolicited AEs during 28 days post each vaccination |

| | |
|---|---|
| | ▪ Occurrence of SAEs, MAAEs and AESIs during the whole study period<br>▪ (Only in Sentinel group) Occurrence of out-of-normal range clinical laboratory test results (including change from baseline values) during 7 days post 1st vaccination |
| **Secondary Endpoints** | |
| **Objectives** | **Endpoints** |
| To assess the immunogenicity of GBP510 vaccines in healthy younger adults post each vaccination | ▪ GMT of IgG antibody to the SARS-CoV-2 RBD measured by ELISA<br>▪ GMFR of IgG antibody to the SARS-CoV-2 RBD from baseline measured by ELISA<br>▪ Percentage of participants with ≥ 4-fold rise from baseline in ELISA IgG titer<br>▪ GMT of neutralizing antibody to the SARS-CoV-2 measured by pseudovirus and wild-type virus neutralization assays<br>▪ GMFR of neutralizing antibody to the SARS-CoV-2 from baseline measured by pseudovirus and wild-type virus neutralization assays<br>▪ Percentage of participants with ≥ 4-fold rise from baseline in pseudovirus and wild-type neutralizing antibody titer<br>▪ Cell-mediated response for both Th1 and Th2 (e.g. INF-γ, IL-4 using ELISpot or other system) |
| **Exploratory Endpoints** | |
| To conduct various exploratory studies on samples collected from study participants to further evaluate the safety and/or immunogenicity profile of GBP510 vaccines | |

**For Stage 2**

| **Primary Endpoints** |
|---|

| Objectives | Endpoints |
|---|---|
| To assess the immunogenicity of GBP510 vaccines in healthy younger and older adults post each vaccination | ▪ GMT of IgG antibody to the SARS-CoV-2 RBD measured by ELISA<br>▪ GMFR of IgG antibody to the SARS-CoV-2 RBD from baseline measured by ELISA<br>▪ Percentage of participants with ≥ 4-fold rise from baseline in ELISA IgG titer<br>▪ GMT of neutralizing antibody to the SARS-CoV-2 measured by pseudovirus and wild-type virus neutralization assays<br>▪ GMFR of neutralizing antibody to the SARS-CoV-2 from baseline measured by pseudovirus and wild-type virus neutralization assays<br>▪ Percentage of participants with ≥ 4-fold rise from baseline in pseudovirus and wild-type neutralizing antibody titer<br>▪ Cell-mediated response for both Th1 and Th2 (e.g. INF-γ, IL-4 using ELISpot or other system) |
| **Secondary Endpoints** | |
| To assess the reactogenicity and safety profile of GBP510 vaccines in healthy younger and older adults post each vaccination | ▪ Occurrence of immediate systemic reactions<br>▪ Occurrence of solicited local AEs during 7 days post each vaccination<br>▪ Occurrence of solicited systemic AEs during 7 days post each vaccination<br>▪ Occurrence of unsolicited AEs during 28 days post each vaccination<br>▪ Occurrence of SAEs, MAAEs and AESIs during the whole study period |
| **Exploratory Endpoints** | |
| To conduct various exploratory studies on samples collected from study participants to further evaluate the safety and/or immunogenicity profile of GBP510 vaccines | |

**Overall Design:**

This is a first-in-human, Phase I/II, randomized, placebo-controlled, observer-blinded, age-escalating study to assess the safety, reactogenicity and immunogenicity of a SK SARS-CoV-2 recombinant protein nanoparticle vaccine (GBP510) adjuvanted with or without AS03 in healthy younger and older adults.

A total of 320 healthy younger and older adults will be enrolled and block-randomized at a 2:1:1 ratio for both Stage 1 (within each dose-level cohort) and Stage 2, to receive 2 doses of either one GBP510 formulation with AS03 (Test group 1 or 3), or without AS03 (Test group 2 or 4), or placebo saline (Placebo group). Test group 2 will only be included in Stage 1.

This study will consist of 2 stages, and a stepwise approach will be adopted as a safety precaution. Approximately 80 healthy adults aged 19 to 55 years will be enrolled and vaccinated first in Stage 1, and blinded safety data collected through 7 days after the 1st study vaccination will be reviewed by the sponsor, and then by the independent DSMB in an unblinded manner. Advancement to Stage 2 for further enrollment of 240 healthy younger and older adults aged 19 to 85 years will be determined if an acceptable safety profile is confirmed based on the sponsor and DSMB review. DSMB will recommend whether to proceed to the next stage or not, and DSMB may suggest discontinuation of the study or adjustment of dose and dosing regimen based on the safety review. The 2nd vaccination in Stage 2 will be initiated if a safety profile on the 1st and/or 2nd vaccination in all Stage 1 and 2 participants accumulated by approximately 1 week before the first 2nd vaccination in Stage 2 is confirmed as appropriate by the sponsor and DSMB review.

Over the study period, participants will attend 10 planned visits. Telephone calls will be made 7 days after each vaccination (Day 7+3 after Visit 2 and Visit 4). However, sentinel participants will be required to return at Day 7(+ 3 days) after 1st vaccination for rigorous safety assessment.

Study vaccination will comprise 2 intramuscular injections of saline placebo, or a 10 or 25μg dose of GBP510 adjuvanted with or without AS03 in an injection volume of approximately 0.5mL. The study vaccines will be injected preferably into the deltoid muscle of the upper arm at a 28-day interval.

Halting rules based on reactogenicity and safety outcomes are defined, and enrollment and study vaccination may be paused during the study if any halting rules are met.

**Brief Summary:** The purpose of this study is to assess the safety, reactogenicity and immunogenicity of a SK SARS-CoV-2 recombinant protein nanoparticle vaccine adjuvanted with or without AS03 in healthy younger and older adults.

**Number of Participants:**

- In Stage 1, each dose-level cohort will comprise a minimum of 40 adult participants (20 participants in Test group 1 or 3, 10 participants in Test group 2 or 4, and Placebo group) aged between 19 and 55 years. The 8 sentinel participants (4 participants in Test group 1 or 3, 2 participants in Test group 2 or 4, and Placebo group) per each dose-level cohort will be assigned for the 1st study vaccination. Administration of the remaining 32 participants in each dose-level cohort (16 participants in Test group 1 or 3, 8 participants in Test group 2 or 4, and

Placebo group) will commence a minimum of 7 days after completion of the 1st study vaccination in the 8 sentinel participants. The DSMB will review 7-day safety data of the 1st vaccination from sentinel participants to recommend further administration. Escalation to a higher dose-level cohort will also be determined based on the DSMB review of at least 7-day safety data of the 1st study vaccination from sentinel participants in the lower dose-level cohort.

- In Stage 2, approximately 80 adult participants aged between 19 and 85 years will be enrolled in Test group 1 and 3, along with 40 adult participants in Test group 4 and Placebo group. Approximately 20% of the participants in each treatment group will be the elderly population aged between 65 and 85 years, and foreigners including non-Asian ethnicity will be allowed for participation. All Test groups and Placebo group will be enrolled and vaccinated in parallel.

**Intervention Groups and Duration:**

This study includes 2-dose schedule (28-day interval) of low and high dose levels of GBP510.

**[Stage 1] 19 to 55 years old**

| Cohort | Treatment Group | Formulation | N (Sentinel) |
|---|---|---|---|
| Low dose-level | Test group 1 | GBP510 adjuvanted with AS03 (RBD 10ug/dose); a total injection volume of 0.5mL | 20 (4) |
| | Test group 2 | GBP510 (RBD 10ug/dose); a total injection volume of 0.5mL | 10 (2) |
| | Placebo group | Placebo saline (0.5mL) | 10 (2) |
| High dose-level | Test group 3 | GBP510 adjuvanted with AS03 (RBD 25ug/dose); a total injection volume of 0.5mL | 20 (4) |
| | Test group 4 | GBP510 (RBD 25ug/dose); a total injection volume of 0.5mL | 10 (2) |
| | Placebo group | Placebo saline (0.5ml) | 10 (2) |

**[Stage 2] 19 to 85 years old (including the elderly ≥65 years old)**

| Treatment Group | Formulation | N (Elderly) |
|---|---|---|
| Test group 1 | GBP510 adjuvanted with AS03 (RBD 10ug/dose); a total injection volume of 0.5mL | 80 (16) |
| Test group 3 | GBP510 adjuvanted with AS03 (RBD 25ug/dose); a total injection volume of 0.5mL | 80 (16) |

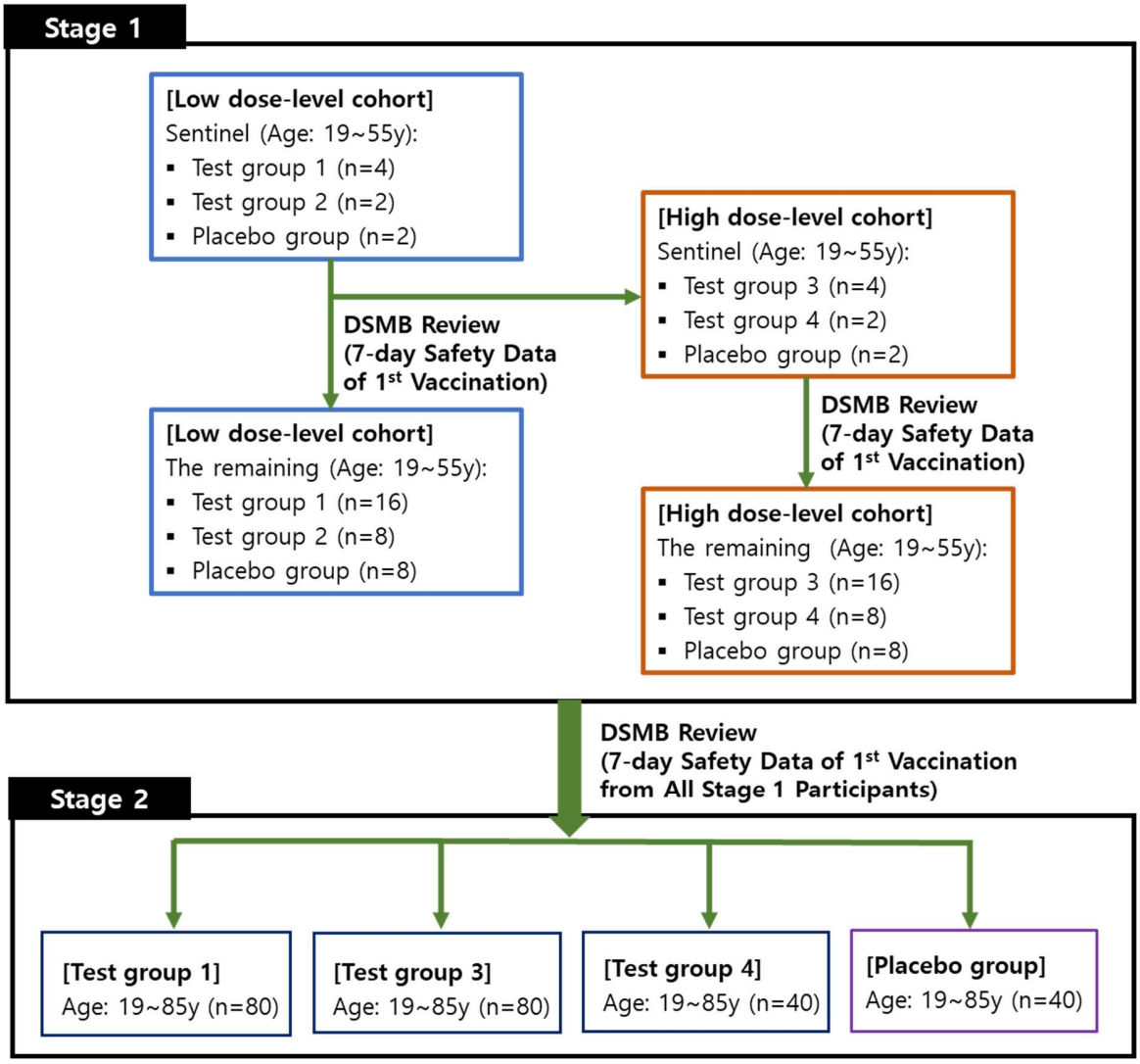
| | | |
|---|---|---|
| Test group 4 | GBP510 (RBD 25ug/dose); a total injection volume of 0.5mL | 40 (8) |
| Placebo group | Placebo saline (0.5ml) | 40 (8) |

Participants are expected to participate for up to a maximum of approximately 14 months. 12 months study follow-up after 2nd vaccination will be conducted.

**Data Monitoring/Other Committee**

An independent DSMB will be organized before study initiation. An unblinded review by DSMB will be performed as halting rules are met, any safety concerns arise during this study, or to recommend further enrollment (non-sentinel participants), and advancement to the next dose level or next stage (i.e. Stage 1→2).

## 1.2. Schema


Stage 1
[Low dose-level cohort]
Sentinel (Age: 19~55y):
▪ Test group 1 (n=4)
▪ Test group 2 (n=2)
▪ Placebo group (n=2)
DSMB Review
(7-day Safety Data
of 1st Vaccination)
[High dose-level cohort]
Sentinel (Age: 19~55y):
▪ Test group 3 (n=4)
▪ Test group 4 (n=2)
▪ Placebo group (n=2)
DSMB Review
(7-day Safety Data
of 1st Vaccination)
[Low dose-level cohort]
The remaining (Age: 19~55y):
▪ Test group 1 (n=16)
▪ Test group 2 (n=8)
▪ Placebo group (n=8)
[High dose-level cohort]
The remaining (Age: 19~55y):
▪ Test group 3 (n=16)
▪ Test group 4 (n=8)
▪ Placebo group (n=8)
DSMB Review
(7-day Safety Data of 1st Vaccination
from All Stage 1 Participants)
Stage 2
[Test group 1]
Age: 19~85y (n=80)
[Test group 3]
Age: 19~85y (n=80)
[Test group 4]
Age: 19~85y (n=40)
[Placebo group]
Age: 19~85y (n=40)

## 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 | Visit 10 | Unscheduled[@] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit description | Screening | Vaccination 1 | 1-week Follow up | | Vaccination 2 | 1-week Follow up (Telephone Contact) | 2-week Follow up | 4-week Follow up | 3-month Follow up | 6-month Follow up | 12-month Follow up | |
| | | | Sentinel group | Others (Telephone Call) | | | | | | | | |
| Visit windows (days) | 0 to 28 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 84±7 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 | X | X |
| 12-lead ECG : *Only for Sentinel group* | X | | X | | | | | X | | | | X |
| Chest radiograph | X | | X | | | | | X | | | | X |
| Laboratory test[§] (hematology, clinical chemistry, serology) | X (20mL) | | X (20mL) | | | | | X (20mL) | | | | X |
| Laboratory test (urine) : *Only for Sentinel group* | 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 | X | X |
| Medical History | X | X[†] | | | | | | | | | | |
| Prior and concomitant medications | X | X[†] | X | X | X[†] | X | X | X | X | X | X | X |
| Inclusion/exclusion criteria | X | X[†] | | | | | | | | | | |
| Obtain randomization number and study intervention allocation | | X | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Blood sampling for SARS-CoV-2 immunogenicity (ELISA, NAb) | SR01‡ (15mL) | | | | SR02‡ (15mL) | | SR03 (15mL) | SR04 (15mL) | SR05 (15mL) | SR06 (15mL) | SR07 (15mL) | |
| Blood sampling for SARS-CoV-2 immunogenicity (CMI): Only for the participants randomly selected | WB01‡ (32mL) | | | | WB02 (32mL) | | WB03 (32mL) | WB04 (32mL) | | | | |
| Study Vaccination | | X | | | X | | | | | | | |
| Immediate Adverse Reaction (2-hour monitoring for Sentinel group, 30 minutes for others) | | X | | | X | | | | | | | |
| Provide and explain participant diary completion methods (paper or e-diary) | | X* (1st diary) | | | X* (2nd diary) | | | X* (3rd diary) | | | | |
| Provide the participant with thermometer and rulers | | X | | | | | | | | | | |
| Review participant diary (paper or e-diary) | | | X** | X** | X** | X** | X** | X** | | | | X |
| Collect participant diary (only for paper participant diary) | | | | | X (1st diary) | | | X (2nd diary) | | | X (3rd diary) | |
| Collect solicited local and systemic AEs | | X | X | X | X | X | | | | | | X |
| Collect unsolicited AEs | | X | X | X | X | X | X | X | | | | X |
| Collect SAE, MAAE and AESI | | X | X | X | X | X | X | X | X# | X# | X# | X |
| Collect COVID-19 related information | | X | X | 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

† Mandatory before vaccination.

§ Among the laboratory tests, serology test will be conducted only at screening

‡ Blood samples should be collected before study vaccination. SR01 and WB01 samples may be collected along with the blood samples for laboratory and/or serum pregnancy tests before randomization, if the participant prefers to reduce venipunctures. SR01 and WB01 samples will be discarded if the participant screen-failed. The blood volume for SR01~07 samples can be reduced down to 10mL for the elderly participants aged 65 and 85 years.

* If e-diary is applicable, study staff should assist the participant in downloading the e-diary application onto the participant's own device at Visit 2, and remind to continuously record the e-diary at Visit 4. If paper diary is used, 1st, 2nd and 3rd paper diary will be provided to the participant at Visit 2, 4 and 7 respectively.
** If e-diary is used, ongoing safety review will be performed from Visit 2 to 10. If a paper diary was provided, the participant will be asked to bring the diary with them as he or she returns to the site for Visit 3 to 10. Site staff should remind the participant to keep recording the diary during the visits.
#During these visits, the staff will review whether the participant experienced any SAE, MAAE, AESI (including pIMDs) or COVID-19 related events not yet reported through e-diary or paper diary. If e-diary is used, study staff may help the participant remove e-diary application from participant's device at Visit 10.
@ Activities to be performed in unscheduled visits are optional, and can be chosen at the investigator's discretion.

# 2. Introduction

## 2.1. Study Rationale

This is a first-in-human study to evaluate, safety, reactogenicity and immunogenicity of GBP510 adjuvanted with or without AS03 in healthy younger and older adults. The GBP510 vaccine is intended to provide protection against infection with SARS-CoV-2, and the clinical dose was determined based on the non-clinical immunogenicity and toxicity profile.

## 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 65 million cases of COVID-19 including a million deaths have been reported from over 221 countries and territories around the world as of today.[1][2]

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 are the only preventive measures to block the transmission of SARS-CoV-2, which causes an enormous socioeconomic impact.

Therefore, development of a COVID-19 vaccine is urgent and crucial to elicit individual and herd immunity to prevent the transmission of SARS-CoV-2. WHO announced that 51 vaccine candidates are in the clinical stage as of Dec 2$^{nd}$, 2020. Most of the vaccine candidates under development are targeting the S protein, using different technologies including mRNA, DNA, protein, and viral vectored vaccines.[3]

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 safety and product stability. Also, SK bioscience has solid clinical experience with this construct and expression system in the development of various vaccines including human papillomavirus vaccine. Based on such previous experiences, 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 that was developed by GlaxoSmithKline will be 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.

## 2.3. Benefit/Risk Assessment

### 2.3.1. Risk Assessment

The GBP510 vaccine has not been studied in human, and currently only non-clinical study data is available. However, the immunogenicity and safety profiles of the protein nanoparticle vaccine candidates in clinical-stage development or other vaccines using similar expression system which have been developed by SK bioscience, as well as the large safety database of AS03 derived from use of the pandemic influenza vaccine may support a favorable risk/benefit profile of GBP510.

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

Otherwise, previous data from studies of SARS or MERS and other respiratory viruses suggested that poorly neutralizing anti-SARS-CoV-2 antibody responses could potentially exacerbate COVID-19 through vaccine-associated enhanced disease (VAED), reason why such antibody responses, as well as the occurrence and severity of SARS-CoV-2 infections will be rigorously evaluated in all participants during the whole study.

The potential risks of participating in this trial are those associated with vaccination or having blood drawn. 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.

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) are adverse events of special interest (AESI) undergoing special safety monitoring for vaccines containing Adjuvant Systems including AS03. 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. pIMD is an AESI and will be collected until study end.

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).

### 2.3.2. Benefit Assessment

There is no direct benefit to the participants. However, most of participants will have chances to receive the GBP510 vaccine which may be effective to prevent SARS-CoV-2 infection. Furthermore, participants will contribute to development of a potential COVID-19 vaccine.

# 3. Objectives and Endpoints

**For Stage 1**

| **Primary Endpoints** | |
|---|---|
| **Objectives** | **Endpoints** |
| To assess the reactogenicity and safety profile of GBP510 vaccines in healthy younger adults post each vaccination | ▪ Occurrence of immediate systemic reactions<br>▪ Occurrence of solicited local AEs during 7 days post each vaccination<br>▪ Occurrence of solicited systemic AEs during 7 days post each vaccination<br>▪ Occurrence of unsolicited AEs during 28 days post each vaccination<br>▪ Occurrence of SAEs, MAAEs and AESIs during the whole study period<br>▪ (Only in Sentinel group) Occurrence of out-of-normal range clinical laboratory test results (including change from baseline values) during 7 days post 1st vaccination |
| **Secondary Endpoints** | |
| **Objectives** | **Endpoints** |
| To assess the immunogenicity of GBP510 vaccines in healthy younger adults post each vaccination | ▪ GMT of IgG antibody to the SARS-CoV-2 RBD measured by ELISA<br>▪ GMFR of IgG antibody to the SARS-CoV-2 RBD from baseline measured by ELISA<br>▪ Percentage of participants with ≥ 4-fold rise from baseline in ELISA IgG titer<br>▪ GMT of neutralizing antibody to the SARS-CoV-2 measured by pseudovirus and wild-type virus neutralization assays<br>▪ GMFR of neutralizing antibody to the SARS-CoV-2 from baseline measured by pseudovirus and wild-type virus neutralization assays<br>▪ Percentage of participants with ≥ 4-fold rise from baseline in pseudovirus and wild-type neutralizing antibody titer |

| | |
|---|---|
| | ▪ Cell-mediated response for both Th1 and Th2 (e.g. INF-γ, IL-4 using ELISpot or other system) |
| **Exploratory Endpoints** | |
| To conduct various exploratory studies on samples collected from study participants to further evaluate the safety and/or immunogenicity profile of GBP510 vaccines | |

**For Stage 2**

| **Primary Endpoints** | |
|---|---|
| **Objectives** | **Endpoints** |
| To assess the immunogenicity of GBP510 vaccines in healthy younger and older adults post each vaccination | ▪ GMT of IgG antibody to the SARS-CoV-2 RBD measured by ELISA<br>▪ GMFR of IgG antibody to the SARS-CoV-2 RBD from baseline measured by ELISA<br>▪ Percentage of participants with ≥ 4-fold rise from baseline in ELISA IgG titer<br>▪ GMT of neutralizing antibody to the SARS-CoV-2 measured by pseudovirus and wild-type virus neutralization assays<br>▪ GMFR of neutralizing antibody to the SARS-CoV-2 from baseline measured by pseudovirus and wild-type virus neutralization assays<br>▪ Percentage of participants with ≥ 4-fold rise from baseline in pseudovirus and wild-type neutralizing antibody titer<br>▪ Cell-mediated response for both Th1 and Th2 (e.g. INF-γ, IL-4 using ELISpot or other system) |
| **Secondary Endpoints** | |
| To assess the reactogenicity and safety profile of GBP510 vaccines in healthy younger and older adults post each vaccination | ▪ Occurrence of immediate systemic reactions<br>▪ Occurrence of solicited local AEs during 7 days post each vaccination |

| | |
|---|---|
| | ▪ Occurrence of solicited systemic AEs during 7 days post each vaccination<br>▪ Occurrence of unsolicited AEs during 28 days post each vaccination<br>▪ Occurrence of SAEs, MAAEs and AESIs during the whole study period |
| **Exploratory Endpoints** | |
| To conduct various exploratory studies on samples collected from study participants to further evaluate the safety and/or immunogenicity profile of GBP510 vaccines | |

# 4. Study Design

## 4.1. Overall Design

This is a first-in-human, Phase I/II, randomized, placebo-controlled, observer-blinded, age-escalating study to assess the safety, reactogenicity and immunogenicity of a SK SARS-CoV-2 recombinant protein nanoparticle vaccine (GBP510) adjuvanted with or without AS03 in healthy younger and older adults.

A total of 320 healthy younger and older adults will be enrolled and block-randomized at a 2:1:1 ratio for both Stage 1 (within each dose-level cohort) and Stage 2, to receive 2 doses of either one GBP510 formulation with AS03 (Test group 1 or 3), or without AS03 (Test group 2 or 4), or placebo saline (Placebo group). Test group 2 will only be included in Stage 1.

This study will consist of 2 stages, and a stepwise approach will be adopted as a safety precaution. Approximately 80 healthy adults aged 19 to 55 years will be enrolled and vaccinated first in Stage 1, and blinded safety data collected through 7 days after the 1st study vaccination will be reviewed by the sponsor, and then by the independent DSMB in an unblinded manner. Advancement to Stage 2 for further enrollment of 240 healthy younger and older adults aged 19 to 85 years will be determined if an acceptable safety profile is confirmed based on the sponsor and DSMB review. DSMB will recommend whether to proceed to the next stage or not, and DSMB may suggest discontinuation of the study or adjustment of dose and dosing regimen based on the safety review. The 2nd vaccination in Stage 2 will be initiated if a safety profile on the 1st and/or 2nd vaccination in all Stage 1 and 2 participants accumulated by approximately 1 week before the first 2nd vaccination in Stage 2 is confirmed as appropriate by the sponsor and DSMB review

- In Stage 1, each dose-level cohort will comprise a minimum of 40 adult participants (20 participants in Test group 1 or 3, 10 participants in Test group 2 or 4, and Placebo group) aged between 19 and 55 years. The 8 sentinel participants (4 participants in Test group 1 or 3, 2 participants in Test group 2 or 4, and Placebo group) per each dose-level cohort will be assigned for the 1st study vaccination. Administration of the remaining 32 participants in each dose-level cohort (16 participants in Test group 1 or 3, 8 participants in Test group 2 or 4, and Placebo group) will commence a minimum of 7 days after completion of the 1st study vaccination in the 8 sentinel participants. The DSMB will review 7-day safety data of the 1st vaccination from sentinel participants to recommend further administration. Escalation to a higher dose-level cohort will also be determined based on the DSMB review of at least 7-day safety data of the 1st study vaccination from sentinel participants in the lower dose-level cohort.

- In Stage 2, approximately 80 adult participants aged between 19 and 85 years will be enrolled in Test group 1 or 3, along with 40 adult participants in Test group 4 and Placebo group. Approximately 20% of the participants in each treatment group will be the elderly population aged between 65 and 85 years, and foreigners including non-Asian ethnicity will be allowed for participation. All Test groups and Placebo group will be enrolled and vaccinated in parallel.

Study vaccination will comprise 2 intramuscular injections of saline placebo, or a 10 or 25μg dose of GBP510 adjuvanted with or without AS03 in an injection volume of approximately 0.5mL. The study vaccines will be injected preferably into the deltoid muscle of the upper arm at a 28-day interval.

**Table 1. Study cohort/ Treatment group**

**[Stage 1] 19 to 55 years old**

| Cohort | Treatment Group | Formulation | N (Sentinel) |
|---|---|---|---|
| Low dose-level | Test group 1 | GBP510 adjuvanted with AS03 (RBD 10ug/dose); a total injection volume of 0.5mL | 20 (4) |
| | Test group 2 | GBP510 (RBD 10ug/dose); a total injection volume of 0.5mL | 10 (2) |
| | Placebo group | Placebo saline (0.5mL) | 10 (2) |
| High dose-level | Test group 3 | GBP510 adjuvanted with AS03 (RBD 25ug/dose); a total injection volume of 0.5mL | 20 (4) |
| | Test group 4 | GBP510 (RBD 25ug/dose); a total injection volume of 0.5mL | 10 (2) |
| | Placebo group | Placebo saline (0.5ml) | 10 (2) |

**[Stage 2] 19 to 85 years old (including the elderly ≥65 years old)**

| Treatment Group | Formulation | N (Elderly) |
|---|---|---|
| Test group 1 | GBP510 adjuvanted with AS03 (RBD 10ug/dose); a total injection volume of 0.5mL | 80 (16) |
| Test group 3 | GBP510 adjuvanted with AS03 (RBD 25ug/dose); a total injection volume of 0.5mL | 80 (16) |
| Test group 4 | GBP510 (RBD 25ug/dose); a total injection volume of 0.5mL | 40 (8) |
| Placebo group | Placebo saline (0.5ml) | 40 (8) |

Over the study period, participants will attend 10 planned visits. Telephone calls will be made 7 days after each vaccination (Day 7+3 after Visit 2 and Visit 4). However, sentinel participants in Stage 1 will be required to return at Day 7(+ 3 days) after 1st vaccination for rigorous safety assessment.

Halting rules based on reactogenicity and safety outcomes are defined, and study vaccination may be paused during the study if any halting rules are met.

An independent DSMB will be organized before study initiation. An unblinded review by DSMB will be performed as halting rules are met, any safety concerns arise during this study, or to recommend further enrollment (non-sentinel participants) and advancement to the next dose level or next stage (i.e. Stage 1→2).

## 4.2. Scientific Rationale for Study Design

This study is designed as a 2-stage, placebo-controlled, randomized, observer-blinded study. Unblinded study staff will be assigned for preparation and administration of study intervention as GBP510 formulation and placebo saline are different in appearance. Additionally, an independent DSMB will be formed and allowed to review safety data in an unblinded manner, which will facilitate ongoing safety monitoring.

## 4.3. Justification for Dose

The multiple doses of GBP510 10μg and 25μg for this study were determined based on the following studies in order to confirm the most effective dose in humans.

A multiple-dose toxicity study was conducted, and GBP510 was well tolerated as 30μg was intramuscularly injected to Sprague-Dawley Rats. Also, a non-human primate study was performed by IPD and the 25ug dose of RBD nanoparticle was administered. High binding and neutralizing antibodies were elicited by vaccination, and notably, no significant abnormality was reported.

## 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. For Stage 1, participant must be 19 to 55 years of age inclusive, at the time of signing the informed consent.
   For Stage 2, participant must be 19 to 85 years of age inclusive, at the time of signing the informed consent

**Type of Participant and Disease Characteristics**

2. Participants who are healthy 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.

**Weight**

4. Body mass index (BMI) within the range 18-30 $kg/m^2$ at screening (inclusive)

**Sex and Contraceptive/Barrier Requirements**

5. 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 10.4 for detailed contraceptive methods)
6. Female participants with a negative urine or serum pregnancy test at screening

**Informed Consent**

7. 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. History of virologically-confirmed COVID-19 disease, or definite or suspected exposure to anyone known to have SARS-CoV-2 infection
3. History of virologically-confirmed SARS or MERS disease
4. History of congenital, hereditary, acquired immunodeficiency, or autoimmune disease
5. Any positive test results for hepatitis B, C, or HIV at screening
6. History of bleeding disorder or thrombocytopenia which is contraindicating intramuscular vaccination in the investigator's opinion
7. History of hypersensitivity and severe allergic reaction (e.g. anaphylaxis, Guillain-Barre syndrome) to any vaccines or components of the study intervention
8. History of malignancy within 5 years prior to the 1st study vaccination
9. Significant chronic illness that, in the opinion of the investigator, might increase risk of severe COVID-19, or interfere with the evaluation of the study objectives (e.g. asthma, chronic pulmonary disease, cardiovascular disease, chronic liver disease, uncontrolled diabetes mellitus or hypertension, renal disorders)
10. History of, or planned surgery under general anesthesia from 1 year prior to the 1st study vaccination through the study period
11. Any other conditions which, in the opinion of the investigator, might interfere with the evaluation of the study objectives (e.g. neurologic or psychiatric conditions)
12. Female participants who are pregnant or breastfeeding
13. (Only for Stage 1) Current smokers or a recent smoking history within 12 weeks prior to the 1st study vaccination. Occasional smokers who smoke up to 10 cigarettes per month may be allowed to participate at the investigator's discretion

**Prior/Concomitant therapy**

14. Receipt of any medications or vaccinations intended to prevent COVID-19.
15. 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
16. Receipt of immunoglobulins and/or any blood or blood products within 12 weeks prior to the 1st study vaccination
17. 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**

18. Participation in another clinical study involving study intervention within 6 months prior to the 1st study vaccination, or concurrent, planned participation in another clinical study with study intervention during this study period.

**Other Exclusions**

19. Investigators, or study staff who are directly involved in the conduct of this study or supervised by the investigator, and their respective family members.
20. Healthcare worker or emergency response personnel in an occupation with a high risk of exposure to SARS-CoV-2

## 5.3. Lifestyle Considerations

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. 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 feasibility criteria for participation in this study, re-screening may be conducted under a different participant number.

## 5.5. Criteria for Temporarily Delaying

If a participant experiences the following conditions, the investigator will 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), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

## 6.1. Study Intervention(s) Administered

| | | |
|---|---|---|
| **Intervention Name** | SARS-CoV-2 Recombinant Protein Nanoparticle Vaccine (GBP510) | Saline placebo |
| **Type** | Vaccine | Placebo |
| **Dose Formulation** | A self-assembling protein nanoparticle displaying RBD of SARS-CoV-2 on the exterior surface | Normal saline (0.9% sodium chloride solution) |
| **Unit Dose Strength(s)** | GBP510 adjuvanted with or without AS03 (RBD 10ug or 25ug/dose); a total injection volume of 0.5mL | NA |
| **Dosage Level(s)** | GBP510 (solely injected): SARS-CoV-2 RBD nanoparticle 10μg, 25μg per 0.5 mL<br>GBP510 (for mixing with AS03): SARS-CoV-2 RBD nanoparticle 10μg, 25μg per 0.25 mL<br>AS03:0.25mL | NA |
| **Route of Administration** | Intramuscular injection | Intramuscular injection |
| **Storage Condition** | 2~8℃ | 1~30℃ |
| **Use** | Experimental | Placebo |
| **IMP and NIMP** | IMP | IMP |
| **Sourcing** | Provided centrally by the sponsor | Provided centrally by the sponsor |
| **Packaging and Labeling** | Study intervention will be provided in 1 or 2 vials, each containing 0.65mL of antigen presentation (GBP510) alone, or 0.35mL of | Study intervention will be provided in 20mL ample. Packages |

| | | |
|---|---|---|
| | GBP510 and 3mL of adjuvant (AS03) respectively. Packages will be labeled as required per country requirement | will be labeled 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, and request authorization for use.
- The investigator or designee must confirm the appropriate labeling of study intervention by the legal requirements.
- Only participants enrolled 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 Pharmacy 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 national regulation. One dose (RBD 10μg or 25μg) of GBP510 will be dispatched in an antigen vial with or without one adjuvant vial containing AS03. The label will state “Investigational Product for clinical trial use only”.

Saline placebo will be supplied as per the standard commercial packaging. The primary and secondary package 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 saline placebo (0.5mL), a GBP510 (RBD 10ug or 25ug per dose) to be mixed with AS03 or without AS03 (a total injection volume of 0.5mL). For reconstituting a GBP510 vaccine adjuvanted with AS03 at 1:1 ratio, 0.35mL will be withdrawn from a vial containing approximately 3mL of AS03, and put in another vial containing 0.35mL of GBP510 (RBD 10ug or 25ug per dose). For each injection, 0.5mL will be withdrawn from any of the vials containing solely 0.65mL of GBP510, or 0.7mL of GBP510 mixed with AS03, or the ample with 20mL of normal saline. The residual volume in the vial or ample will be discarded.

The study vaccines will be injected preferably into the deltoid muscle of the upper arm at a 28-day interval (Day 0, 28).

Study intervention will be administered by qualified unblinded site personnel (i.e. unblinded study vaccinators) according to the Pharmacy 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

On the day of enrollment in Stage 1, participants who meet the inclusion/exclusion criteria and sign the ICF will be randomly assigned to Test group 1 or 3 / Test group 2 or 4 / Placebo group in a 2:1:1 ratio to have approximatively 80 participants (20 participants in Test group 1 or 3, 10 participants in Test group 2 or 4, and Placebo group of each dose-level cohort). For Stage 2, participants will be randomized in a 2:2:1:1 ratio to have approximatively 240 participants (80 participants in Test group 1 or 3, 40 participants in Test group 4 and Placebo group). Test group 2 will only be included in Stage 1.

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 trial site in Stage 1, and by age (< 65 or ≥65 years), race, and trial site in Stage 2 to pursue an approximately equal distribution of participants between the treatment groups within each age group, race, and trial site.

Enrollment will proceed in a staged fashion.
Dosing of sentinel participants in Stage 1 will begin with 8 participants in the low dose-level cohort (4 participants in Test group 1, 2 participants in Test group 2 and Placebo group). The additional 8 sentinel participants in the high dose-level cohort (4 participants in Test group 3, 2

participants in Test group 4 and Placebo group) will be enrolled at least 7 days after the 1st administration of the 8 sentinel participants in the low dose-level cohort, based on DSMB recommendation. Likewise, if the DSMB has determine safety data is acceptable at least 7 days after the first 8 sentinel participants have received the 1st administration, then further enrollment will proceed with the remaining 32 participants in each dose-level cohort (16 participants in Test group 1 or 3, and 8 participants in Test group 2 or 4, and Placebo group).

The DSMB will also recommend whether to discontinue the study or proceed to Stage 2 based on 7-day safety profile of GBP510 adjuvanted with or without AS03 after the 1st study vaccination in Stage 1.

### 6.3.2. Blinding

This study will be observer-blinded between the GBP510 formulations and placebo.

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 placebo saline or either of the GBP510 formulations with or without adjuvant since each GBP510 formulation and placebo saline 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 treatment of the participant. Investigators may also be asked to unblind the code for a participant who is eligible to receive an authorized COVID-19 vaccine. Participants have a right to request code-breaking prior to receiving an available licensed COVID-19 vaccine, and the investigator should provide medical advice and information on potential risks and opportunities associated with COVID-19 vaccination. Particularly, if the participant is identified to have received the GBP510 vaccine, the investigator should inform the participant that available data on benefit and risk of booster or cross-vaccination with different COVID-19 vaccines is insufficient (see Section 9.5).

A participant who has been unblinded for other COVID-19 vaccination will be encouraged to remain in the study, and complete all scheduled activities for safety and immunogenicity evaluations. The investigator should carefully monitor the participants if any SAEs or AESIs occur as a potential result of booster and/or cross-vaccination. All safety and immunogenicity data collected from the unblinded participants will be separately analyzed, and more details will be described in the Statistical Analysis Plan (SAP).

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 and CRF.
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 without AS03 in a vial, or placebo saline. 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 CRF. If a participant fails to receive the study intervention as planned, the reason should also be recorded.

## 6.5. Dose Modification

The decision to proceed to the next dose level of GBP510 25μg will be made by the sponsor and DSMB based on safety and reactogenicity data obtained in 8 sentinel participants at the prior dose level in Stage 1.

## 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. Over-the-counter drugs, herbals, vitamins, and supplements will also be collected. 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 CRF. 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 will not be withdrawn from the study, and required to return at scheduled visits for 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, protocol deviation, or at request of participant. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for safety. 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 CRF.

## 7.2. Participant Discontinuation/Withdrawal from the Study

Participants have 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 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 or sponsor due to significant non-compliance with the protocol (i.e. refused / 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 CRF.

A participant who discontinues from the study will be encouraged to complete all scheduled safety follow-ups per 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. All attempts to contact the participant and information collected during contacts 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. Sentinel participants in Stage 1 (4 participants in either of Test group 1 or 3, 2 participants in either of Test group 2 or 4, and each Placebo group) should be observed at least 2 hours after each vaccination. 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 8.1.9.

### 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.

After each vaccination, participants will be provided with either of a paper or electronic participant diary (downloaded on participant's own device), 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 CRF.

Participants will be instructed to report any solicited AE with grade 3 or 4, using the e-diary or telephone contact during 7 days after each vaccination, and the investigator or designee should contact the participant to obtain further details to confirm the severity grade and determine whether a site visit is clinically required. If a participant experiences a confirmed grade 3 or 4 solicited reaction determined to be related to the study vaccine, the investigator should immediately notify the sponsor, and discuss discontinuation of further vaccination.

### 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 e-diary or telephone contact. If any unsolicited AE with grade 3 or 4 is reported, the investigator or designee should contact the participant to confirm the severity and ask the participant to return to the trial site if deemed necessary.

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 4 and 5).

### 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: Priority List of Adverse Events of Special Interest-COVID-19.[5]

**Table 2. AESI relevant to COVID-19**

| Body System | AESI relevant to COVID-19 |
|---|---|
| **Immunologic** | Enhanced disease following immunization<br>Anaphylaxis<br>Vasculitides |
| **Respiratory** | Acute respiratory distress syndrome (ARDS) |
| **Cardiac** | Acute cardiac injury including:<br>▪ Microangiopathy<br>▪ Heart failure and cardiogenic shock<br>▪ Stress cardiomyopathy<br>▪ Coronary artery disease<br>▪ Arrhythmia<br>▪ Myocarditis, pericarditis |
| **Hematologic** | Coagulation disorder:<br>▪ Deep vein thrombosis<br>▪ Pulmonary embolus<br>▪ Cerebrovascular stroke<br>▪ Limb ischemia<br>▪ Hemorrhagic disease<br>▪ Thrombocytopenia |
| **Renal** | Acute kidney injury |
| **Gastrointestinal** | Liver injury |
| **Neurologic** | Guillain Barré Syndrome<br>Generalized convulsion<br>Anosmia, ageusia<br>Meningoencephalitis<br>Acute disseminated encephalomyelitis |
| **Dermatologic** | Chilblain-like lesions<br>Single organ cutaneous vasculitis<br>Erythema multiforme |

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 3.

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 3, 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 above diagnoses will be available to investigators at study start.

**Table 3. List of Potential Immune-mediated Diseases**

| **Neuroinflammatory disorders** | **Musculoskeletal disorders** | **Skin disorders** |
|---|---|---|
| • Cranial nerve neuropathy, including paralysis and paresis (eg, Bell's palsy).<br>• Optic neuritis.<br>• Multiple sclerosis.<br>• Transverse myelitis.<br>• Guillain-Barré syndrome, including Miller Fisher syndrome and other variants.<br>• Acute disseminated encephalomyelitis, including site specific variants, eg, noninfectious encephalitis, encephalomyelitis, myelitis, myeloradiculoneuritis.<br>• Myasthenia gravis, including Lambert-Eaton myasthenic syndrome.<br>• Demyelinating peripheral neuropathies including:<br>- Chronic inflammatory demyelinating polyneuropathy.<br>- Multifocal motor neuropathy.<br>- Polyneuropathies associated with monoclonal gammopathy.<br>• Narcolepsy. | • Systemic lupus erythematosus and associated conditions.<br>• Systemic scleroderma (systemic sclerosis), including:<br>- Diffuse scleroderma.<br>- CREST syndrome.<br>• Idiopathic inflammatory myopathies, including:<br>- Dermatomyositis.<br>- Polymyositis.<br>• Anti-synthetase syndrome.<br>• Rheumatoid arthritis and associated conditions including:<br>- Juvenile idiopathic arthritis.<br>- Still's disease.<br>• Polymyalgia rheumatica.<br>• Spondyloarthropathies, including:<br>- Ankylosing spondylitis.<br>- Reactive arthritis (Reiter's syndrome).<br>- Undifferentiated spondyloarthritis.<br>- Psoriatic arthritis.<br>- Enteropathic arthritis.<br>• Relapsing polychondritis.<br>• Mixed connective tissue disorder.<br>• Gout. | • Psoriasis.<br>• Vitiligo.<br>• Erythema nodosum.<br>• Autoimmune bullous skin diseases (including pemphigus, pemphigoid, and dermatitis herpetiformis).<br>• Lichen planus.<br>• Sweet's syndrome.<br>• Localized scleroderma (morphea). |
| **Vasculitis** | **Blood disorders** | **Others** |

| | | |
|---|---|---|
| • Large vessels vasculitis including:<br>- Giant cell arteritis (temporal arteritis).<br>- Takayasu's arteritis.<br>• Medium sized and/or small vessels vasculitis including:<br>- Polyarteritis nodosa.<br>- Kawasaki's disease.<br>- Microscopic polyangiitis.<br>- Wegener's granulomatosis (granulomatosis with polyangiitis).<br>- Churg–Strauss syndrome (allergic granulomatous angiitis or eosinophilic granulomatosis with polyangiitis).<br>- Buerger's disease (thromboangiitis obliterans).<br>- Necrotizing vasculitis (cutaneous or systemic).<br>- Anti neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified).<br>- Henoch-Schonlein purpura (IgA vasculitis).<br>- Behcet's syndrome.<br>- Leukocytoclastic vasculitis. | • Autoimmune hemolytic anemia.<br>• Autoimmune thrombocytopenia.<br>• Antiphospholipid syndrome.<br>• Pernicious anemia.<br>• Autoimmune aplastic anemia.<br>• Autoimmune neutropenia.<br>• Autoimmune pancytopenia. | • Autoimmune glomerulonephritis including:<br>- IgA nephropathy.<br>- Glomerulonephritis rapidly progressive.<br>- Membranous glomerulonephritis.<br>- Membranoproliferative glomerulonephritis.<br>- Mesangioproliferative glomerulonephritis.<br>- Tubulointerstitial nephritis and uveitis syndrome.<br>• Ocular autoimmune diseases including:<br>- Autoimmune uveitis.<br>- Autoimmune retinitis.<br>• Autoimmune myocarditis.<br>• Sarcoidosis.<br>• Stevens-Johnson syndrome.<br>• Sjögren's syndrome.<br>• Alopecia areata.<br>• Idiopathic pulmonary fibrosis.<br>• Goodpasture syndrome.<br>• Raynaud's phenomenon. |
| **Liver disorders** | **Gastrointestinal disorders** | **Endocrine disorders** |
| • Autoimmune hepatitis.<br>• Primary biliary cirrhosis.<br>• Primary sclerosing cholangitis.<br>• Autoimmune cholangitis. | • Inflammatory bowel disease, including:<br>- Crohn's disease.<br>- Ulcerative colitis.<br>- Microscopic colitis.<br>- Ulcerative proctitis.<br>• Celiac disease.<br>• Autoimmune pancreatitis. | • Autoimmune thyroiditis (Hashimoto thyroiditis).<br>• Grave's or Basedow's disease.<br>• Diabetes mellitus type 1.<br>• Addison's disease.<br>• Polyglandular autoimmune syndrome.<br>• Autoimmune hypophysitis. |

### 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.[6]

**Table 4. 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 5. Solicited Systemic AE Grading Scale**

| Systemic (General) | Mild (Grade 1) | Moderate (Grade 2) | Severe (Grade 3) | Potentially Life Threatening (Grade 4) |
|---|---|---|---|---|
| **Fever(°C)** | 38.0-38.4 | 38.5-38.9 | 39.0-40 | >40 |
| **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 | ER visit or hospitalization |

| | | | | |
|---|---|---|---|---|
| | | | outpatient IV hydration | |
| **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 6. 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 disappearance 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 12 weeks after the last study vaccination (Visit 8, Day 84±7 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 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 record form, within 24 hours of the investigator's awareness.
Follow-up will be conducted to obtain additional information on the pregnancy and its 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, 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 inform the relevant health authorities and investigators of any reportable SAEs 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 tympanic temperature.

### 8.1.13. Electrocardiogram (ECG)

A routine 12-lead ECG will be performed only in sentinel participants at time points specified in the SoA (Section 1.3) to measure the parameters including ventricular rate, PR interval, QRS duration, and QT/QTc interval. ECGs may be repeated for quality reasons (e.g. muscle movements or electrode dislocation).
The investigator or designee will interpret the results, and report any clinically significant abnormal findings as AEs during the study or as baseline conditions at screening. Any ECG abnormal changes will be monitored carefully until the measurements return to normal (or clinically insignificant degree). Unscheduled ECGs may be collected by the investigator for safety reasons.

### 8.1.14. Chest Radiograph

Chest radiograph will be performed at time points specified in the SoA (Section 1.3), and any clinically significant abnormal findings will be recorded as AEs after study vaccination. The investigator or designee may perform additional chest radiographs until the abnormality resolves or stabilizes.

### 8.1.15. Clinical Safety Laboratory Assessments

Clinical laboratory tests including hematology, clinical chemistry, urine and other tests (i.e. serology, serum or urine pregnancy tests) will be performed by either the central laboratory or each site laboratory. Clinical laboratory tests will be conducted in all participants, except for urine test, which will be performed only in sentinel participants.

The investigator must review the laboratory report, document this review, and record any clinically significant changes outside normal range occurring during the study as an AE. The laboratory reports must be filed with the source documents. Abnormal laboratory findings associated with the underlying disease will not be considered clinically significant unless judged by the investigator to be more severe than expected for the participant's condition.

Biological safety endpoints will be assessed on samples for hematology, clinical chemistry, and urine tests, which are collected from sentinel participants at Visit 1, 3, and 7. Biological safety endpoints will be defined as either within or outside normal ranges provided by the laboratory, and assessed on whether or not they reach the pre-defined severity levels.

See Appendix 10.2 for the potential list and pre-defined severity scale of clinical laboratory tests to be performed, and the SoA (Section 1.3) for the timing and frequency.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor. If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.

## 8.2. COVID-19 Disease Surveillance

If a participant experiences a suspicious symptom of COVID-19 (e.g. cough, sore throat), or is notified as having a potential contact with COVID-19 patients, the participant should take examination according to The Central Disaster Safety and Countermeasure Headquarters' guidelines. The participant will be instructed to contact the investigator immediately to notify the fact that the symptoms occurred, and if the participant's condition permits, the participant will be recommended to return to the trial site for necessary examinations and observation.

If the 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 either telephone or e-diary (if applicable), 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 (including electronic diary)

An e-diary application will be installed on the participant's own device, and 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.

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. E-diary may allow recording of each information only within a pre-defined timeframe. 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 CRF.
Data reported in the e-diary will be available for review by investigators, the sponsor, and DSMB members. Investigators or designee will be required to review e-diary data online at frequent intervals, ideally on daily basis, as part of the ongoing safety review.

## 8.3. Halting Rules

The investigator or designee, and the sponsor will monitor the reactogenicity and safety data on an ongoing basis to immediately identify any event that may contributes to a halting rule.

The study vaccinations will be paused if any of the following events occur, and pending for subsequent review by the DSMB for recommendation of further vaccination, including a second dose. All other routine activities for the participants who completed all study vaccinations will continue even during the pause.

- Any death occurred during the whole study period after study vaccination
- An SAE occurred during the whole study period which is assessed by the investigator as related to study vaccine
- Any grade 3 or 4 solicited local or systemic AE, in the same single term, occurred in more than 15% of cumulative participants (more than 9 participants at any dose level in Stage 1, more than 30 participants at any dose level in Stage 2), within 7 days after each study vaccination (1$^{st}$ and 2$^{nd}$ vaccination will be assessed separately).
- Any grade 3 or 4 unsolicited AE, in the same preferred term (by MedDRA), occurred in more than 15% of cumulative participants (more than 9 participants at any level in Stage 1, more than 30 participants at any dose level in Stage 2), within 7 days after each study vaccination, which is assessed by the investigator as related to study vaccine.

## 8.4. 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.

### 8.4.1. Immunogenicity Assessments

Blood samples will be collected for the following assays. PRNT and 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 neutralization assay using SARS-CoV-2 pseudovirus (PBNA): PBNA (Pseudovirion-based Neutralization Assay) is an assay to measure the neutralizing antibody titers by using PsV (Pseudovirus). PsV is formed with major protein which induces the immunogenicity of target virus as an envelope protein, and contains proper reporter gene such as luciferase. After PsV infection, the neutralizing antibody titer can be measured by the expression level of reporter gene from infected cells. For example, PBNA50 shows the expression level of 50% reduced which means the neutralization rate of 50%.
- SARS-CoV-2 serum neutralization assay using SARS-CoV-2 wild-type virus (PRNT) : PRNT (Plaque Reduction Neutralization Test) is the assay for the assessment of neutralizing antibodies in serum that are induced after viral infection or vaccination by using wild-type viruses. By measuring the plaque form of CPE (Cytopathic Effect) that appears when the virus (SARS-CoV-2 wild-type virus) infects cells, it is assessed how much infectious virus can have been protected by counting the reduction of the plaques
- Cellular immunology assay using ELISpot, or other system : ELISpot (Enzymelinked Immuno-Spot) 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 and infectious pathogens such as viruses and bacteria. Representative cytokines in relation to the Th1 response are IFN-γ, whereas ones in relation to the Th2 responses are the IL-4. The biotinylated cytokine specific monoclonal antibodies for detection antibodies are using to bind the target cytokines such as IFN-γ and IL-4, streptavidin-ALP conjugates and BCIP/NBT-plus substrate are used for color development the spots.

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

| | **Visit 2 (pre-** | **Visit 4 (pre-** | **Visit 6** | **Visit 7** | **Visit 8** | **Visit 9** | **Visit 10** |
|---|---|---|---|---|---|---|---|

| | 1st dose) | 2nd dose) | (2-week Follow up) | (4-week Follow up) | (3-month Follow up) | (6-month Follow up) | (12-month Follow up) |
|---|---|---|---|---|---|---|---|
| **ELISA / Neutralization assay** | Serum | Serum | Serum | Serum | Serum | Serum | Serum |
| **Cellular immunology assay** | Whole blood | Whole blood | Whole blood | Whole blood | | | |

### 8.4.2. 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.

## 8.5. Study Procedures

### 8.5.1. Visit 1 - Screening

- 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 IRT 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 (body 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 chest radiograph
- (Only for sentinel participants) Perform a 12-lead ECG
- (Only for sentinel participants) Collect a urine sample for clinical laboratory test (urine test)
- Collect a blood sample (approximately 20mL) for clinical laboratory tests (hematology, clinical chemistry and serology tests)
- Blood sample may be collected along with the blood samples for laboratory and/or serum pregnancy tests before randomization, if the participant prefers to reduce venipunctures. Samples will be discarded if the participant screen-failed.
- 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
- Complete the source document and eCRF

### 8.5.2. 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 (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
- Check screening chest radiograph and 12-lead ECG (if applicable).
- Check screening laboratory test results including hematology, clinical chemistry, serology and urine (if applicable) tests
- 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°C) 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.
- (In case of blood sample was not taken during Visit 1) Collect a blood sample (a maximum of 47mL) for immunogenicity assessment. A maximum of 15mL (10mL recommended for the elderly participants aged between 65 and 85 years) will be collected to obtain serum samples

for ELISA and neutralizing Ab assay, and 32mL will be collected to harvest PMBC for ELISpot assay (or for other system).

- Unblinded study vaccinator will administer 1 dose of study intervention preferably into the deltoid muscle of the upper arm (see the Pharmacy Manual). Details of dosing information including the date and site of injection 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. In case of sentinel participants (4 participants in either of Test group 1 or 3, 2 participants in either of Test group 2 or 4, and each Placebo group), blinded site staff should observe them at least 2 hours after vaccination.
- 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 participant diary according to the type of tool.
  - If e-diary is applicable, explain how to use the e-diary application to record local and systemic reactions, and concurrent medications. Assist the participant in downloading the e-diary application onto the participant's own device.
  - Alternatively, a paper diary can be provided and explained to the participant if the participant has difficulties in using the e-diary application.
- Ask the participant to contact the site staff if the participant experience any of the following symptoms within 7 days after administration. Any medically attended events (e.g. emergency room visit), hospitalization, or COVID-19 related events should be immediately notified as well.
  - Fever ≥39°C
  - Redness or swelling at injection site > 10cm
  - Severe pain at the injection site
  - Any other severe systemic symptoms
- 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 participant's mobile device on which the e-diary application was downloaded or the paper participant diary for Visit 4.

  In case of sentinel participants, the next visit should be scheduled 7 days later (Visit 3, Day 7+3 after Visit 2).
- Complete the source document and eCRF.

### 8.5.3. Visit 3 – 1-week Follow up (Day 7+3 after Visit 2)

**For sentinel participants in Stage 1:**

- The first 7-day reactogenicity data after 1st vaccination will be reviewed based on participant

diary. For participants using e-diary application, the investigator or designee should perform ongoing safety review, and daily review is ideal.

If reactogenicity 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 (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
- Perform a chest radiograph
- Perform a 12-lead ECG
- Collect a blood sample (approximately 20mL) and urine sample for clinical laboratory tests (hematology, clinical chemistry and urine tests)
- 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 participant diary.
- Remind the female participant of childbearing potential to maintain appropriate contraception.
- Arrange an appointment for the next study visit (Visit 4, Day 28+5 after Visit 2), and remind the participant to bring back participant's mobile device or the paper participant diary.
- Complete the source document and eCRF.

**For non-sentinel participants in Stage 1 & All participants in Stage 2:**

- 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 participant's mobile device or the paper participant diary for the next visit (Visit 4, Day 28+5 after Visit 2).
- Complete the source document and eCRF.

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

- Review the safety data after 1st vaccination based on participant diary. If a paper diary was used, retrieve the 1st participant diary.

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 (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. 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.
- Collect a blood sample (a maximum of 15mL) to obtain serum samples for ELISA and neutralizing Ab assay, and 32mL will be collected to harvest PMBC for ELISpot assay (or for other system).
- Unblinded study vaccinator will administer 1 dose of study intervention preferably into the deltoid muscle of the upper arm (see the Pharmacy Manual). Details of dosing information including the date and site of injection should be recorded.
- Keep the participant under medical observation for at least 30 minutes (at least 2 hours for sentinel participants) after administration, and record any acute reactions in the source document.
- Remind the participant to continue recording participant diary. If a paper diary was used, distribute a 2nd paper copy.
- Ask the participant to contact the site staff if the participant experience any of the following symptoms within 7 days after administration. Any medically attended events (i.e. emergency room visit) or hospitalization. COVID-19 related events should be immediately notified as well.
  - Fever ≥39℃
  - Redness of swelling at injection site > 10cm
  - Severe pain at the injectino site
  - Any other severe systemic symptoms
- Remind the female participant of childbearing potential to maintain appropriate contraception.
- 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 participant's mobile device on which the e-diary application was downloaded or the paper participant diary for Visit 6.
- Complete the source document and eCRF.

### 8.5.5. 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 participant's mobile device or the paper participant diary for the next study visit (Day 14+3 after Visit 4).
- Complete the source document and eCRF.

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

- Review the safety data after 2nd vaccination based on 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 (a maximum of 47mL) for immunogenicity assessment. A maximum of 15mL will be collected to obtain serum samples for ELISA and neutralizing Ab assay, and 32mL will be collected to harvest PMBC for ELISpot assay (or for other system)
- 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 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 participant's mobile device or the paper participant diary.
- Complete the source document and eCRF.

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

- Review the safety data after 2nd vaccination based on participant diary. If a paper diary was provided, retrieve the 2nd participant diary.

  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 (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
- Perform a chest radiograph
- (Only for sentinel participants) Perform a 12-lead ECG
- (Only for sentinel participants) Collect a urine sample for clinical laboratory test (urine test)
- Collect a blood sample (approximately 20mL) for clinical laboratory tests (hematology and clinical chemistry tests)
- Collect a blood sample (a maximum of 47mL) for immunogenicity assessment. A maximum of 15mL will be collected to obtain serum samples for ELISA and neutralizing Ab assay, and 32mL will be collected to harvest PMBC for ELISpot assay (or for other system)
- Remind the participant to continue recording participant diary to report MAAEs, SAEs, and COVID-19 related events. If a paper diary was used, distribute a 3rd paper copy.
- 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 84±7 after Visit 4)
- Remind the female participant of childbearing potential to use appropriate contraceptive methods
- Complete the source document and eCRF.

### 8.5.8. Visit 8 – 3-month Follow up (Day 84±7 after Visit 4)

- Review and record SAEs, MAAEs, AESIs (including pIMDs), or COVID-19 related events occurred since the previous visit based on 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.
- 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
- Perform urine or serum pregnancy test only in a female participant of childbearing potential.
- Collect a blood sample for immunogenicity assessment. A maximum of 15mL will be collected to obtain serum samples for ELISA and neutralizing Ab assay.
- 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 168±14 after Visit 4)
- Complete the source document and eCRF.

### 8.5.9. Visit 9 – 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 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.
- 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
- Collect a blood sample for immunogenicity assessment. A maximum of 15mL will be collected to obtain serum samples for ELISA and neutralizing Ab assay.
- 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 10, Day 365±14 after Visit 4)
- Complete the source document and eCRF.

### 8.5.10. Visit 10 – 12-month Follow up (Day 365±14 after Visit 4)

- Review and record SAEs, MAAEs, AESIs (including pIMDs), or COVID-19 related events occurred since the previous visit based on 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.
- 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
- Collect a blood sample for immunogenicity assessment. A maximum of 15mL will be collected to obtain serum samples for ELISA and neutralizing Ab assay.
- Assist the participant to remove the e-diary application from the participant's own device, if it is still installed. If a paper diary was used, retrieve the 3rd participant diary.
- Complete the source document and eCRF.

# 9. Statistical Considerations

## 9.1. Statistical Hypotheses

This study is not designed to test any hypotheses. All analyses will be descriptive.

## 9.2. Sample Size Determination

Each Test group in this study will comprise 10, 50, or 100 participants, depending on its dose level and presence of adjuvant. Assuming a drop-out rate of approximately 10%, at least 9, 45, or 90 evaluable participants are anticipated for each Test group. This sample size is based on clinical considerations to achieve the objectives of the study, and it may not be able to demonstrate rare AEs. If the true AE rate is 5%, with 100 participants in a test group, there is 99.41% probability of observing at least 1 AE. Table 7 presents the probabilities of observing at least one particular AE given various true event rates.

**Table 7**. Probability of Observing at Least One AE for various event rates.

| True Event Rate | n=4 | n=10 | n=20 | n=40 | n=50 | n=60 | n=80 | n=100 | n=200 | n=260 |
|---|---|---|---|---|---|---|---|---|---|---|
| 0.1% | 0.40 | 1.00 | 1.98 | 3.92 | 4.88 | 5.83 | 7.69 | 9.52 | 18.14 | 22.90 |
| 0.5% | 1.99 | 4.89 | 9.54 | 18.17 | 22.17 | 25.97 | 33.04 | 39.42 | 63.30 | 72.84 |
| 1.0% | 3.94 | 9.56 | 18.21 | 33.10 | 39.50 | 45.28 | 55.25 | 63.40 | 86.60 | 92.67 |
| 2.0% | 7.76 | 18.29 | 33.24 | 55.43 | 63.58 | 70.24 | 80.14 | 86.74 | 98.24 | 99.48 |
| 3.0% | 11.47 | 26.26 | 45.62 | 70.43 | 78.19 | 83.92 | 91.26 | 95.24 | 99.77 | 99.96 |
| 4.0% | 15.07 | 33.52 | 55.80 | 80.46 | 87.01 | 91.36 | 96.18 | 98.31 | 99.97 | >99.99 |
| 5.0% | 18.55 | 40.13 | 64.15 | 87.15 | 92.31 | 95.39 | 98.35 | 99.41 | >99.99 | >99.99 |
| 7.0% | 25.19 | 51.60 | 76.58 | 94.51 | 97.34 | 98.71 | 99.70 | 99.93 | >99.99 | >99.99 |
| 10.0% | 34.39 | 65.13 | 87.84 | 98.52 | 99.48 | 99.82 | 99.98 | >99.99 | >99.99 | >99.99 |
| 15.0% | 47.80 | 80.31 | 96.12 | 99.85 | 99.97 | 99.99 | >99.99 | >99.99 | >99.99 | >99.99 |
| 20.0% | 59.04 | 89.26 | 98.85 | 99.99 | >99.99 | >99.99 | >99.99 | >99.99 | >99.99 | >99.99 |
| 30.0% | 75.99 | 97.18 | 99.92 | >99.99 | >99.99 | >99.99 | >99.99 | >99.99 | >99.99 | >99.99 |
| 40.0% | 87.04 | 99.40 | >99.99 | >99.99 | >99.99 | >99.99 | >99.99 | >99.99 | >99.99 | >99.99 |
| 50.0% | 93.75 | 99.90 | >99.99 | >99.99 | >99.99 | >99.99 | >99.99 | >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 results assessments. 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, and have no major protocol deviations.<br>Two PPS will be defined as below:<br>▪ PPS1 for Primary stage (Visit 1 to 7)<br>▪ PPS2 for Extension stage (Visit 8 to 10)<br>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 7 (Day 28+5 after Visit 4) did not produce valid test results.<br>▪ Participant did not meet all inclusion criteria or met at least one of the exclusion criteria<br>▪ Participant did not complete the vaccination schedule<br>▪ Preparation and / or administration of study intervention was not done as per-protocol<br>▪ Participant did not receive the study intervention in the proper time window<br>▪ Any of the blood samples were not drawn, or not drawn in the proper time window until Visit 7 (Day 28+5 after Visit 4)<br>▪ Participant received a protocol-prohibited medication or vaccine from Visit 2 (Day 0) to Visit 7 (Day 28+5 after Visit 4) (see Section 6.7.1)<br>In addition to the reasons listed above, participants will also be excluded from the PPS2 if any of their additional blood samples from Visit 8 (Day 84±7 after Visit 4) to Visit 10 (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 primary analysis and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

### 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. Safety Analyses

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
- 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, 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.
- (Only for Sentinel group) Clinical safety laboratory parameters at Visit 1, 3, and 7 will be summarized by severity. Laboratory values and their relative changes will also be presented.

### 9.4.3. Immunogenicity Analyses

Immunogenicity analyses will be performed on the PPS 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 in ELISA will be calculated based on Clopper-Pearson method.
If appropriate, subgroup or covariate-adjusted analyses may be performed. These subgroups / covariates may include pre-vaccination antibody titer, baseline demographics and other baseline characteristics. More details and potential further analyses may be described in the Statistical Analysis Plan (SAP).

- GMT of IgG antibody to the SARS-CoV-2 RBD measured by ELISA at the following time points : before and 4 weeks after 1st vaccination, 2, 4 weeks, 3, 6 and 12 months after 2nd vaccination
- GMFR of IgG antibody to the SARS-CoV-2 RBD from baseline measured by ELISA at the following time points : 4 weeks after 1st vaccination, 2, 4 weeks, 3, 6, and 12 months after 2nd vaccination
- Percentage of participants with ≥ 4-fold rise from baseline in ELISA IgG titer at the following time points : 4 weeks after 1st vaccination, 2, 4 weeks, 3, 6, and 12 months after 2nd vaccination
- GMT of neutralizing antibody to the SARS-CoV-2 measured by pseudovirus and wild-type virus neutralization assays at the following time points : before and 4 weeks after 1st vaccination, 2, 4 weeks, 3, 6 and 12 months after 2nd vaccination
- GMFR of neutralizing antibody to the SARS-CoV-2 from baseline measured by pseudovirus and wild-type virus neutralization assays at the following time points : 4 weeks after 1st vaccination, 2, 4 weeks, 3, 6, and 12 months after 2nd vaccination
- Percentage of participants with ≥ 4-fold rise from baseline in pseudovirus and wild-type neutralizing antibody titer at the following time points : 4 weeks after 1st vaccination, 2, 4 weeks, 3, 6, and 12 months after 2nd vaccination
- Cell-mediated response for both Th1 and Th2 (e.g. INF-γ, IL-4 using ELISpot or other system) at the following time points : before 1st vaccination, 4 weeks after 1st vaccination, 2, 4 weeks after 2nd vaccination

### 9.4.4. Other Analyse(s)

Any further analyses will be described in the SAP.

## 9.5. Interim and Primary Analyses

An interim analysis of the demographics, safety and immunogenicity data collected from participants in Stage 1 up to Visit 7 (Day 28+5 after Visit 4) will be performed once an interim database lock has been conducted. Likewise, the primary analysis will be performed on demographics, safety and immunogenicity data obtained from participants in Stage 1 and 2 up to Visit 7 (Day 28+5 after Visit 4).

The blind will be broken for these analyses, and the randomization schedule will be provided to investigators and other blinded study staff, except for the laboratory personnel performing the immunogenicity tests. The laboratory personnel will remain blind to treatment group assigned until final database lock after Visit 10 (Day 365±14 after Visit 4).

The sponsor may provide the investigators with summary of individual IgG, neutralization antibody titers, and cell-mediated immune responses post-vaccination after the interim and/or primary analyses, in order to allow them to consult with participants for future vaccination with

other licensed COVID-19 vaccines. The investigators should inform the participants of potential risk and benefit of booster or cross-vaccination with different COVID-19 vaccines is insufficient.

# 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) Guidelines
- Applicable local laws and regulations including KGCP

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 MFDS 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 secure 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

Participant safety will be continuously monitored by the DSMB, which includes safety signal detection at any time during the study.

In addition, an early aggregated safety data review will be performed by the DSMB, the goal of which is to allow for a cautious, stepwise approach to study vaccination. An initial safety review for this study is planned for the first 8 sentinel participants in the low dose-level cohort (4

participants in Test group 1, and 2 participants in Test group 2 and Placebo group) who have provided intensive safety data for 7 days after the 1st study vaccination. Dose escalation to the high dose-level cohort will be determined after review of such 7-day safety data in Stage 1.

Likewise, if the DSMB has recommended safety data is acceptable at least 7 days after the 8 sentinel participants have received the 1st administration in each dose-level cohort of Stage 1, then further enrollment will proceed with the remaining 32 participants in each dose-level cohort (16 participants in Test group 1 or 3, and 8 participants in Test group 2 or 4, and Placebo group).

The DSMB will also recommend whether to discontinue the study before proceeding to Stage 2 according to their medical judgement, based on 7-day safety review after the 1st study vaccination in Stage 1.

In case of the 2nd vaccination in Stage 2, the DSMB will review the safety data of all participants in Stage 1 and 2 after the 1st and/or 2nd vaccination, which has been accumulated until approximately 1 week before the first 2nd vaccination in Stage 2, and recommend whether it is acceptable or not to proceed with the 2nd vaccination in Stage 2 participants.

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 decisions of further enrollment, dose escalation and advancement to the next stage. The 7-day 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 would potentially contribute to a requirement to pause the study vaccination.

- Any death occurred during the whole study period after study vaccination
- An SAE occurred during the whole study period which is assessed by the investigator as related to study vaccine
- Any grade 3 or 4 solicited local or systemic AE, in the same single term, occurred in more than 15% of cumulative participants (more than 9 participants at any dose level in Stage 1, more than 30 participants at any dose level in Stage 2), within 7 days after each study vaccination (1st and 2nd vaccination will be assessed separately).
- Any grade 3 or 4 unsolicited AE, in the same preferred term (by MedDRA), occurred in more than 15% of cumulative participants (more than 9 participants at any level in Stage 1, more than 30 participants at any dose level in Stage 2), within 7 days after each study vaccination, which is assessed by the investigator as related to study vaccine.

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

### 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 KGCP, 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 contact will prevail as to publication rights.

## 10.2. Appendix: Clinical Laboratory Tests

The tests detailed below (but not limited to) may be performed by the central laboratory or each site laboratory at time points defined in the SoA (Section 1.3). Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

| Hematology | Clinical Chemistry | Urine | Others |
|---|---|---|---|
| ▪ WBC<br>▪ RBC<br>▪ Hemoglobin<br>▪ Hematocrit<br>▪ Platelet<br>▪ Differential Count (Neutrophil, Lymphocytes, Eosinophils) | ▪ Glucose<br>▪ AST<br>▪ ALT<br>▪ Alkaline phosphatase (ALP)<br>▪ Total bilirubin<br>▪ Total protein<br>▪ Albumin<br>▪ BUN<br>▪ Creatinine<br>▪ Uric Acid<br>▪ Cholesterol<br>▪ Triglyceride<br>▪ Calcium<br>▪ Phosphorus<br>▪ Sodium<br>▪ Potassium | ▪ Protein<br>▪ Glucose<br>▪ Blood (RBC) | **[Serology]**<br>▪ HIV antibody<br>▪ Hepatitis B surface antigen<br>▪ Hepatitis C virus antibody<br><br>**[Pregnancy test]**<br>▪ Serum or urine hCG pregnancy test (as needed for women of childbearing potential) |

Biological safety endpoints and any other clinically significant abnormal laboratory findings will be evaluated referring to the following severity grading scale, 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.[6]

| | Mild (Grade 1) | Moderate (Grade 2) | Severe (Grade 3) | Potentially Life Threatening (Grade 4) |
|---|---|---|---|---|
| **Hematology** | | | | |
| Hemoglobin (Female) - gm/dL | 11.0 – 12.0 | 9.5 – 10.9 | 8.0 – 9.4 | < 8.0 |
| Hemoglobin (Female) change from baseline | Any decrease – 1.5 | 1.6 – 2.0 | 2.1 – 5.0 | > 5.0 |

| | | | | |
|---|---|---|---|---|
| value - gm/dL Any decrease | | | | |
| Hemoglobin (Male) - gm/dL | 12.5 – 13.5 | 10.5 – 12.4 | 8.5 – 10.4 | < 8.5 |
| Hemoglobin (Male) change from baseline value – gm/dL Any decrease | Any decrease – 1.5 | 1.6 – 2.0 | 2.1 – 5.0 | > 5.0 |
| WBC Increase - cell/mm$^3$ | 10,800 – 15,000 | 15,001 – 20,000 | 20,001 – 25, 000 | > 25,000 |
| WBC Decrease - cell/mm$^3$ | 2,500 – 3,500 | 1,500 – 2,499 | 1,000 – 1,499 | < 1,000 |
| Lymphocytes Decrease - cell/mm$^3$ | 750 – 1,000 | 500 – 749 | 250 – 499 | <250 |
| Neutrophils Decrease - cell/mm$^3$ | 1,500 – 2,000 | 1,000 – 1,499 | 500 – 999 | < 500 |
| Eosinophils - cell/mm$^3$ | 650 – 1500 | 1501 - 5000 | > 5000 | Hypereosinophilic |
| Platelets Decreased - cell/mm$^3$ | 125,000 – 140,000 | 100,000 – 124,000 | 25,000 – 99,000 | < 25,000 |
| **Clinical Chemistry** | | | | |
| Sodium – Hyponatremia mEq/L | 132 – 134 | 130 – 131 | 125 – 129 | < 125 |
| Sodium – Hypernatremia mEq/L | 144 – 145 | 146 – 147 | 148 – 150 | > 150 |
| Potassium – Hyperkalemia mEq/L | 5.1 – 5.2 | 5.3 – 5.4 | 5.5 – 5.6 | > 5.6 |
| Potassium – Hypokalemia mEq/L | 3.5 – 3.6 | 3.3 – 3.4 | 3.1 – 3.2 | < 3.1 |
| Glucose – Hypoglycemia mg/dL | 65 – 69 | 55 – 64 | 45 – 54 | < 45 |

| | | | | |
|---|---|---|---|---|
| Glucose – Hyperglycemia Fasting – mg/dL Random – mg/dL | 100 – 110 110 – 125 | 111 – 125 126 – 200 | >125 >200 | Insulin requirements or hyperosmolar coma |
| Blood Urea Nitrogen BUN mg/dL | 23 – 26 | 27 – 31 | > 31 | Requires dialysis |
| Creatinine – mg/dL | 1.5 – 1.7 | 1.8 – 2.0 | 2.1 – 2.5 | > 2.5 or requires dialysis |
| Calcium – hypocalcemia mg/dL | 8.0 – 8.4 | 7.5 – 7.9 | 7.0 – 7.4 | < 7.0 |
| Calcium – hypercalcemia mg/dL | 10.5 – 11.0 | 11.1 – 11.5 | 11.6 – 12.0 | > 12.0 |
| Phosphorous – hypophosphatemia mg/dL | 2.3 – 2.5 | 2.0 – 2.2 | 1.6 – 1.9 | < 1.6 |
| Albumin – Hypoalbuminemia g/dL | 2.8 – 3.1 | 2.5 – 2.7 | < 2.5 | -- |
| Total Protein – Hypoproteinemia g/dL | 5.5 – 6.0 | 5.0 – 5.4 | < 5.0 | -- |
| Alkaline phosphate – increase by factor | 1.1 – 2.0 x ULN | 2.1 – 3.0 x ULN | 3.1 – 10 x ULN | > 10 x ULN |
| Liver Function Tests –ALT, AST increase by factor | 1.1 – 2.5 x ULN | 2.6 – 5.0 x ULN | 5.1 – 10 x ULN | > 10 x ULN |
| Bilirubin – when accompanied by any increase in Liver Function Test increase by factor | 1.1 – 1.25 x ULN | 1.26 – 1.5 x ULN | 1.51 – 1.75 x ULN | > 1.75 x ULN |
| Bilirubin – when Liver Function Test is normal; increase by factor | 1.1 – 1.5 x ULN | 1.6 – 2.0 x ULN | 2.0 – 3.0 x ULN | > 3.0 x ULN |
| Cholesterol | 201 – 210 | 211 – 225 | > 226 | --- |
| **Urine** | | | | |

| | | | | |
|---|---|---|---|---|
| Protein | Trace | 1+ | 2+ | Hospitalization or dialysis |
| Glucose | Trace | 1+ | 2+ | Hospitalization for hyperglycemia |
| Blood (microscopic) – red blood cells per high power field (rbc/hpf) | 1 - 10 | 11 – 50 | > 50 and/or gross blood | Hospitalization or packed red blood cells (PRBC) transfusion |

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** “ULN” is the upper limit of the normal range.

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

### 10.3.1. 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.<br>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.<br>▪ ADRs are all noxious and unintended responses to study intervention related to any dose of study intervention.<br>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).<br>▪ Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.<br>▪ New conditions detected or diagnosed after study vaccination even though it may have been present before the start of the study.<br>▪ Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. |

| Events NOT 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.<br>▪ 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.<br>▪ 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.

### 10.3.2. 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 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 situations:**

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).

### 10.3.3. 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 is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- 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.

### 10.3.4. 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.

## 10.4. 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.

- Vasectomized male partner (only if the partner is the sole sexual partner of the female particiapnt of childbearing potential)
- Sexual obstinence : 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, inplantable, transdermal, injectable)
- Intrauterine device

## 10.5. 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 |
| BCIP/NBT | Bromochloroindolyl phosphate-Nitro blue tetrazolium |
| BMI | Body Mass Index |
| BUN | Bloodurea Nitrogen |
| CAPA | Corrective Action and Preventive Action |
| CBER | Center for Biologics Evaluation and Research |
| CI | Confidence Interval |
| CIOMS | Council for International Organizations of Medical Sciences |
| CMI | Cell Medicated Immunity |
| CONSORT | Consolidated Standards of Reporting Trials |
| 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 |
| ELISpot | Enzyme-linked ImmunoSpot |

| | |
|---|---|
| ER | Emergency Room |
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |
| FSFV | First Participant's First Visit |
| GCP | Good Clinical Practice |
| GMT | Geometric Mean Titer |
| GMFR | Geometric Mean Fold Rise |
| hCG | Human Chorionic Gonadotropin |
| HEENT | Head Eyes Ears Nose and Throat |
| HIV | Human Immunodeficiency Virus |
| HRP | Horseradish peroxidas |
| IB | Investigator's Brochure |
| ICF | Informed Consent Form |
| ICH | International Council for Harmonization |
| 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 |
| IV | Intravenous |
| KGCP | Korean Good Clinical Practice |
| 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 |
| PBMC | Peripheral blood mononuclear cell |
| PBNA | Pseudovirion-based Neutralisation Assay |
| pIMD | Potential immune-mediated diseases |
| PPS | Per Protocol Set |
| PRNT | Plaque Reduction Neutralization Test |
| PT | Preferred Term |
| RBD | Receptor-binding Domain |
| RBC | Red Blood Cell Count |
| 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 |

# 11. References

[1]. Lu H., Stratton C.W., Tang Y.W. Outbreak of pneumonia of unknown etiology in Wuhan China: the mystery and the miracle. J Med Virol. 2020 Jan 16 doi: 10.1002/jmv.25678.

[2]. WHO coronavirus disease (COVID-19) dashboard (https://covid19.who.int)

[3]. WHO Draft landscape of COVID-19 candidate vaccines (https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines)

[4] Brighton Collaboration: Safety Platform for Emergency Vaccines (SPEAC), Priority List of Adverse Events of Special Interest: COVID-19 (https://brightoncollaboration.us/priority-list-aesi-covid)

[5] U.S. Food and Drug Administration. (2007) Guidance for Industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical. (http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091977.pdf)