15 December 2022
EMA/417990/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

SKYCovion (WD)

International non-proprietary name: gbp510

Procedure No. EMEA/H/C/005998/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of Contents

List of abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Events of Special Interest
ANCA	Anti-Neutrophil Cytoplasmic Antibody
ANCOVA	Analysis of Covariance
ARDS	Acute respiratory distress syndrome
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
BMI	Body Mass Index
BP	Blood Pressure
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CMI	Cell Mediated Immunity
COVID-19	Corona Virus Disease-19
CRF	Case Report Form
CSR	Clinical Study Report
DSMB	Data Safety Monitoring Board
EC	European Commission
ECG	Electrocardiogram
ELISA	Enzyme-linked Immunosorbent Assay
ELISpot	Enzyme-linked ImmunoSpot
EMA	European Medicines Agency
FACS	fluorescence activated cell sorting
FAS	Full Analysis Set
FRNT	focus-reduction neutralisation test
GCP	Good Clinical Practice
GMFR	Geometric Mean Fold Rise
GMT	Geometric Mean Titre
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICS	Intracellular Cytokine Staining
IEC	Independent Ethics Committee
IFN	Interferon
IgG	Immunoglobulin G
IL	Interleukin
ITT	Intention to Treat
LLOQ	Lower Limit of Quantification
LOD	Limit of Detection
MAA	Marketing Authorisation Application
MAAE	Medically Attended Adverse Events
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	Messenger Ribo Nucleic Acid

n	Number of subjects in group
N	Number of subjects
PBMC	Peripheral Blood Mononuclear Cells
PBNA	Pseudovirion-based Neutralisation Assay
pIMD	Potential immune-mediated diseases
PIP	paediatric investigation plan
PP set	Per-Protocol Set
PRNT	Plaque Reduction Neutralisation Test
PT	Preferred Term
RBD	Receptor-binding Domain
RCDC	Reverse Cumulative Distribution Curve
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome-Coronavirus-2
SCR	Seroconversion Rate
SD	Standard Deviation
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
Th1	T helper 1 cell
Th2	T helper 2 cell
TNF	Tumour Necrosis Factor
VAED	Vaccine-associated Enhanced Disease
WBC	Whole Blood Cell Count
WHO	World Health Organisation
wtVNA	wild-type Virus Neutralisation Assay

1. CHMP Recommendations

Based on the review of the data on quality, safety, efficacy, the application for SKYCovion for active immunisation to prevent COVID-19 caused by SARS-CoV2 in individuals 18 years of age and older is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the List of Questions (see section VI).

In addition, satisfactory answers must be given to the "other concerns" as detailed in the List of Questions.

The major objections precluding a recommendation of marketing authorisation pertain to the following principal deficiencies regarding:

Quality

- Control of RBD nanoparticle content and free component A content at release, during storage and after mixing with adjuvant
- Control strategy Drug Product
- Stability Drug Product
- Missing risk evaluation on nitrosamines.
- GMP status of HiTech Health Limited, Ireland, currently this site is not authorised for batch release of vaccines.

New Active substance claim

Conditional marketing authorisation status

Clinical

- Validation of the bio-analytical assay for determination of neutralising antibody titre (FRNT).

1.1. Questions to be posed to additional experts

Not applicable.

1.2. Inspection issues

1.2.1. GMP inspection(s)

N/A

1.2.2. GCP inspection(s)

N/A

1.3. New active substance status

Based on the review of the data, it is considered that the active substance RBD nanoparticle/Recombinant COVID-19 subunit nanoparticle contained in the medicinal product SKYCovion is not to be qualified as a new active substance in itself. A major objection is raised to the insufficient NAS claim. The major objection is detailed in the List of Questions.

1.4. Additional data exclusivity /Marketing protection

Not applicable.

1.5. Similarity with authorised orphan medicinal products

Not applicable.

1.6. Derogation(s) from market exclusivity

Not applicable.

2. Executive summary

2.1. Problem statement

2.1.1. Disease or condition

SKYCovion is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

In December 2019, the World Health Organisation (WHO) was informed about a cluster of cases of viral pneumonia of unknown cause in Wuhan, China. In mid-January 2020, the pathogen causing this atypical pneumonia was identified as a novel coronavirus, severe acute respiratory coronavirus 2 (SARS-CoV-2) and genome sequence data were published. Since then, the virus has spread globally.

On 30 January 2020, the WHO declared the outbreak a Public Health Emergency of International Concern and on 11 March 2020, a pandemic. The pandemic is ongoing despite unprecedented efforts to control the outbreak.

2.1.2. Epidemiology and risk factors

As of October 2022, there have been over 619 million confirmed cases of SARS-CoV-2 infection globally, with approximately 6.54 million deaths resulting from infection and subsequent coronavirus disease (COVID-19) as registered by WHO (https://covid19.who.int/).

The majority of infections result in asymptomatic or mild disease with full recovery. Underlying health conditions such as hypertension, diabetes, cardiovascular disease, chronic respiratory disease, chronic kidney disease, immune-compromised status, cancer and obesity are considered risk factors for developing severe COVID-19. Other risk factors include organ transplantation and chromosomal abnormalities. Increasing age is another risk factor for severe disease and death due to COVID-19.

2.1.3. Aetiology and pathogenesis

SARS-CoV-2 is a positive-sense single-stranded RNA (+ssRNA) virus with a single linear RNA segment. It is enveloped, and the virions are 50–200 nanometres in diameter. Like other coronaviruses, SARS-CoV-2 has four structural proteins, known as the S (spike), E (envelope), M (membrane), and N (nucleocapsid) proteins.

The spike protein contains a polybasic cleavage site, a characteristic known to increase pathogenicity and transmissibility in other viruses. The Spike is responsible for allowing the virus to attach to and fuse with the membrane of a host cell. The S1 subunit catalyses attachment to the angiotensin-converting enzyme 2 (ACE2) receptor present on cells of the respiratory tract, while the S2 subunit

facilitates fusion with the cell membrane. The spike protein is considered a relevant antigen for vaccine development because it was shown that antibodies directed against it neutralise the virus and it elicits an immune response that prevents infection in animals.

It is believed that SARS-CoV-2 has zoonotic origins, and it has close genetic similarities to bat coronaviruses. Its gene sequence was published in mid-January 2020, and the virus belongs to the beta coronaviruses. Human-to-human transmission of SARS-CoV-2 was confirmed in January 2020.

Transmission occurs primarily via respiratory droplets from coughs and sneezes and through aerosols. The median incubation period after infection to the development of symptoms is four to five days. Most symptomatic individuals experience symptoms within two to seven days after exposure, and almost all symptomatic individuals will experience one or more symptoms before day twelve. Common symptoms include fever, cough, fatigue, breathing difficulties, and loss of smell and taste and symptoms may change over time.

As for all viruses, the SARS-CoV-2 virus will constantly change through mutation and, indeed, many variants of the SARS-CoV-2 virus with different sets of mutations have been observed worldwide. While most emerging SARS-CoV-2 variants will not have a significant impact on the spread of the virus, some mutations or combinations of mutations may provide the virus with a selective advantage, such as increased transmissibility or the ability to evade the host immune response. These variants could increase the risk posed by SARS-CoV-2 to human health and are considered variants of concern (VoC).

2.1.4. Clinical presentation, diagnosis

The severity of COVID-19 disease varies. The disease may take a mild course with few or no symptoms, resembling other common upper respiratory diseases such as the common cold. Mild cases typically recover within two weeks, while those with severe or critical disease may take three to six weeks to recover. Among those who have died, the time from symptom onset to death has ranged from two to eight weeks.

The major complication of severe COVID-19 is acute respiratory distress syndrome (ARDS), presenting with dyspnoea and acute respiratory failure that requires mechanical ventilation. In addition to respiratory sequelae, severe COVID-19 has been linked to cardiovascular sequelae, such as myocardial injury, arrhythmias, cardiomyopathy and heart failure, acute kidney injury often requiring renal replacement therapy, neurological complications such as encephalopathy, and acute ischemic stroke. A distinctive characteristic of SARS-CoV-2 infection is vascular damage, with severe endothelial injury, widespread thrombosis, microangiopathy and angiogenesis.

The gold standard method of testing for presence of SARS-CoV-2 is the reverse transcription polymerase chain reaction (RT-PCR), which detects the presence of viral RNA fragments. As this test detects RNA but not infectious virus, its ability to determine duration of infectivity of patients is limited. The test is typically done on respiratory samples obtained by a nasopharyngeal swab, a nasal swab or sputum sample.

2.1.5. Management

The management of COVID-19 cases has developed since the start of the pandemic, and includes supportive care, which may include fluid therapy, oxygen support, and supporting other affected vital organs. Treatment of hospitalised patients encompass anti-inflammatory agents such as dexamethasone, targeted immunomodulatory agents and anticoagulants as well as antiviral therapy such as Veklury (remdesivir, EMEA/H/C/005622) or Paxlovid (PF-07321332 / ritonavir, EMEA/H/C/005973).

Monoclonal antibodies and notably bi-therapies to overcome potential escape by Variants of Concern (VOC) with mutations on spike are perceived as of potential value. This was particularly true for immunocompromised individuals especially where vaccines might not induce an adequate immune response in those patients of particular medical need. Thus, recently, three monoclonal antibodies, Ronapreve (casirivimab/imdevimab, EMEA/H/C/005814), Regkirona (regdanvimab, EMEA/H/C/005854) and Xevudy (sotrovimab, EMEA/H/C/005676) have been authorised for the treatment of COVID-19 disease in individuals who do not require supplemental oxygen and who are at increased risk of their disease becoming severe. In the case of Ronapreve, it is also authorised for prevention of COVID-19. A fourth monoclonal antibody, Evusheld (tixagevimab / cilgavimab, EMEA/H/C/005788), is approved for the pre-exposure prophylaxis of COVID-19. Other products have been repurposed to be used for the treatment of COVID-19, such as Kineret (anakinra, EMEA/H/C/000363) in adult patients with pneumonia requiring supplemental oxygen (low or high-flow oxygen) who are at risk of progressing to severe respiratory failure determined by plasma concentration of soluble urokinase plasminogen activator receptor (suPAR)≥6 ng/ml, and RoActemra (tocilizumab, EMEA/H/C/000955) in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation.

There are 6 approved vaccines for active immunisation against SARS-CoV-2 aiming to prevent COVID-19 disease: Comirnaty (EMEA/H/C/005735), Spikevax (EMEA/H/C/005791), Vaxzevria (EMEA/H/C/005675), JCovden (EMEA/H/C/005737), Nuvaxovid (EMEA/H/C/005808) and Valneva (EMEA/H/C/006019). In addition, for both Comirnaty and Spikevax, bivalent adapted vaccines were approved in September and October 2022, containing both mRNA coding for the Wuhan strain as well as for an Omicron strain (either BA.1 or BA.4/5). These bivalent adapted vaccines are intended to be used as a booster in persons who have received at least their primary immunisation series.

2.2. About the product

SKYCovion (also referred to in this report as GBP510) is a vaccine developed for the prevention of COVID-19 caused by SARS-CoV-2.

SKYCovion is composed of a recombinant surface antigen protein containing a new nanoparticle targeting the Receptor Binding Domain (RBD) of SARS-CoV-2 Spike (S) protein originated from the parental D614G strain and an adjuvant system (AS03). The addition of the AS03 adjuvant is intended to increase the magnitude of the immune response.

Neutralising antibody response to the parental D614G strain, as well as cellular immune responses (Th1) are elicited following administration of this vaccine, which may contribute to protection against COVID-19.

SKYCovion is to be given as two separate doses of 0.5 mL each. It is recommended to administer the second dose 4 weeks (28 days) after the first dose.

SKYCovion is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. The use of this vaccine should be in accordance with official recommendations.

2.3. The development programme/compliance with guidance/scientific advice

The clinical development programme aims to evaluate the safety and immunogenicity of GBP510 administered as two doses intramuscularly (28 days apart) in individuals ⩾18 years. The current application is based on immunogenicity studies only for the primary series; no efficacy studies were submitted. Efficacy is inferred through an immunobridging approach in which GBP510's ability to induce neutralising antibodies is compared with that of a licensed vaccine with established efficacy.

The clinical development program of GBP510 has been discussed with CHMP during scientific advice and several follow-up advices (EMA/SA/0000054558, EMA/SA/0000059587, EMA/SA/0000062495, EMA/SA/0000079836, EMA/SA/0000084970).

Within these advices, the inference of efficacy based on an immunobridging study was discussed and the approach was agreed. Whilst a vaccine based on a similar platform would have been the preferred comparator for such an approach, a protein-based adjuvanted vaccine was not licensed at the start of the pivotal clinical trial for GBP510. Whilst CHMP indicated that demonstrating non-inferior immunogenicity to a licensed mRNA vaccine would be the preferred option, it was agreed that demonstration of the superiority of neutralising antibodies elicited vs. Vaxzevria (ChAdOx1-S) vaccine was an acceptable approach to infer efficacy. It was advised the primary endpoint should be based on both the GMT ratio and seroconversion rates (*Co-Primary*), and the criteria for the comparison would be:

- The lower bound of the 95% confidence interval around the GMT ratio should be at least 1.
- The lower bound of the 95% confidence interval around the difference in seroconversion rates should exceed -5%.

The primary comparison was changed from week 4 post 2nd vaccination to week 2 post 2nd vaccination. This was accepted based on data showing that the median neutralising antibody levels to ChAdOxS-1 were comparable if not higher 2 weeks post dose 2 compared to 4 weeks post dose 2.

The Applicant did not comply with the advice to perform a PCR test at the day of first dosing to secure enrolment of COVID-19 negative subjects (EMA/SA/0000059587); this was based upon a rapid antigen test.

2.4. General comments on compliance with GMP, GLP, GCP

Compliance with GMP

Currently, no grounds that would trigger a GMP inspection have been identified.

It is noted from the manufacturing list that HiTech Health Limited, Ireland is listed as the only site for importation and batch release of commercial product in EEA territory, however, this site is not authorised for batch release of vaccines. A valid GMP certificate for this site should be provided or this site should be replaced by another batch release manufacturer in the dossier.

According to the submitted GMP certificate, issued by the Dutch competent authority following a distant assessment performed in March 2021, the site SK bioscience Co. Ltd (Andong plant) is deemed GMP compliant in relation to the manufacture of immunological and biotechnology products. Therefore, this GMP certificate together with the MHRA inspection report, which has been accepted by the supervisory authority, is considered sufficient to support the inclusion of the site in the dossier. Therefore, no GMP inspection seems necessary in the context of this MAA procedure.

Compliance with GCP:

According to the Applicant, the studies were done in accordance with recommendations with Good Clinical Practice Guidelines and with all national and local requirements that were in place when the study was conducted.

2.5. Type of application and other comments on the submitted dossier

2.5.1. Legal basis

The legal basis for this application refers to: Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

2.5.2. PRIME

Not applicable.

2.5.3. Accelerated assessment

Not applicable.

2.5.4. Conditional marketing authorisation

The Applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of the above-mentioned Regulation based on the following criteria:

- The benefit-risk balance is positive.
- The Applicant considers it likely that they will be able to provide comprehensive data.

  Comprehensive data, including results from non-clinical and clinical studies, are included in this CMA submission. To date, the clinical development program for GBP510 includes one pivotal Phase III study (GBP510_003) and two supportive Phase I/II studies (GBP510_001 and GBP510_002)).

  Interim results from the pivotal Phase III study are available up to the 20th of April 2022, together with a median of 2.5 months follow-up for the safety data. Stage 2 booster study is ongoing and additional data will be provided in the near future. Six-month safety follow-up data and a primary clinical study report (CSR) (9th of February 2022) is available from the supportive study GBP510_002. Further data from Stage 3 of this study will become available in the coming months. A primary CSR (25th February 2022) is available from the supportive study GBP510_001.
- According to the Applicant, unmet medical needs will be addressed, as GBP510 contains a novel two-component self-assembling RBD nanoparticle that has demonstrated an ability to induce significant levels of neutralising antibodies at low dose levels and is considered as a promising alternative to already authorised vaccines. Based on a combination of a novel nanoparticle approach and an established technology of recombinant protein subunit, GBP510 would contribute to fulfil the unmet needs related to the ongoing SARS-CoV-2 pandemic, including the variants of SARS-CoV-2 through a safe and highly immunogenic profile and by allowing an affordable market access from the high productivity expression, based on Chinese hamster ovary (CHO) cell system.
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

  The clinical studies with the GBP510 25 µg adjuvanted with AS03 vaccine candidate are still ongoing; however, in the large Phase III trial the data demonstrated superiority in terms of neutralising antibody GMTs to the comparator vaccine ChAdOx1-S, non-inferiority in SCR and comparable CMI results with an increased Th1 response and Th2 maintained at a low level,

indicating that the totality of the immune response to GBP510 adjuvanted with AS03 is comparable to the comparator. This, together with the acceptable safety profile obtained from 3133 subjects that received at least one dose, supports a positive benefit-risk balance and the availability of GBP510 adjuvanted with AS03 will provide an effective vaccine to help address unmet medical needs and increased demand.

2.5.5. Marketing authorisation under exceptional circumstances

Not applicable.

2.5.6. Additional data exclusivity/ marketing protection

Not applicable.

2.5.7. New active substance status

The Applicant requested the active substance RBD nanoparticle Recombinant COVID-19 subunit nanoparticle contained in the above medicinal product to be considered as a new active substance, as the Applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

An assessment of this claim is appended.

2.5.8. Orphan designation

Not applicable.

2.5.9. Similarity with orphan medicinal products

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the Applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

2.5.10. Information on paediatric requirements

Pursuant to Articles 7, 8 and 30 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0261/2022 on the agreement of a paediatric investigation plan (PIP) and on the granting of a deferral for recombinant COVID-19 subunit nanoparticle (adjuvanted with AS03) (GBP510) (EMEA-003115-PIP01-21) in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council.

At the time of submission of the application, the PIP EMEA-003115-PIP01-21 was not yet completed as some measures were deferred. The completion date for the PIP is December 2026.

The following studies were agreed in the PIP:

- Randomised, observer-blind, controlled study to assess the reactogenicity, safety and immunogenicity of SARS-CoV-2 recombinant protein nanoparticle vaccine (adjuvanted with AS03) (GBP510) in adolescents from 12 years to less than 18 years of age for the prevention of COVID-19.
- Randomised, observer-blind, controlled study including an-open-label non-controlled dose-finding part to assess the reactogenicity, safety and immunogenicity of SARS-CoV-2

recombinant protein nanoparticle vaccine (adjuvanted with AS03) (GBP510) in children from birth to less than 12 years of age for the prevention of COVID-19.

- Open-label study to assess the reactogenicity, safety and immunogenicity and of SARS-CoV-2 recombinant protein nanoparticle vaccine (adjuvanted with AS03) (GBP510) in immunocompromised children from birth to less than 18 years of age for the prevention of COVID-19.

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

The finished product is presented as a suspension containing 25 µg/0.25 mL of recombinant COVID-19 subunit nanoparticle as an active substance. It is accompanied with adjuvant, AS03 which is to be mixed with the antigen in a 1:1 volume ratio at the time of use. AS03 adjuvant is composed of squalene, DL-α-tocopherol and polysorbate 80.

Other ingredients of the antigen are Sodium chloride, Tromethamine, Arginine, Sucrose and Water for injections. Other ingredients of the adjuvant are Sodium chloride, Disodium hydrogen phosphate, Potassium dihydrogen phosphate, Potassium chloride and Water for injections.

Both antigen suspension and adjuvant are available in a multidose vial (type I glass) with a chlorobutyl stopper with an aluminium overseal and a plastic flip-off cap.

3.1.2. Active Substance

3.1.2.1. General Information

The recombinant COVID-19 subunit nanoparticle is a self-assembling, two-component nanoparticle, comprised of 20 trimers of component A and twelve pentamers of component B. The nanoparticle is held together by non-covalent interactions to form a single antigen. Component A protein displays the receptor binding domain (RBD; which is the target antigen) of SARS-Cov2 and is fused to a nanoparticle assembly domain (I53-50A). Component B is a naturally occurring bacterial enzyme that has been modified to assemble into nanoparticles. The Applicant should further justify that Component B, that is not covalent bound, is considered a part of the active substance since it is not a target antigen and only a vehicle to present the antigen and is non-covalently bound (OC). The general information should be expanded with information on the SARS-CoV-2 variant on which the RBD antigen is based, non-proprietary name of component A, and the interactions/bonds between components A and B in the nanoparticle (OC).

3.1.2.2. Manufacture, process controls and characterisation

Manufacture and quality control of Component A, component B and RBD nanoparticles is performed at SK Bioscience, Republic of Korea. The MCB and WCB testing and storage sites should be indicated (OC).

<u>Component A</u>

Component A is manufactured using CHO cells. The upstream process consists of cultivation of CHO cells, harvest and clarification of culture broth. In the downstream process Component A is purified using chromatography steps, UF/DF. Additional details should be provided on the columns, filters and

other materials used and the column lifetime/cycles should be indicated and validated (OC). Adventitious agents are controlled with low pH virus inactivation, virus filtration, and sterile filtration. In-process controls for the downstream process of component A are provided. A clear batch scale definition has not been provided (OC).

CHO cell is used as cell substrate in which an expression vector was transfected containing the receptor binding domain (RBD) part of component A, fused to I53-50A (nanoparticle assembly domain). Single cell cloning was conducted two times. First a master cell bank (MCB) was generated which was used to manufacture phase I/II clinical material. On this MCB 2nd cloning was used to manufacture MCB (MRN3211). From this a WCB was derived that was used to manufacture phase 3 clinical material and the PPQ batches.

The MCBs (MRN3201, MRN3211) and WCB (WRN3211) were characterised and the tests performed and the results are in line with ICH Q5A(R1) and Ph. Eur. 5.2.3. Extended end of production cell (EEPCB) analysis was performed (3 additional passages from commercial production). The cell concentration of the CHO MCB selected for the stock storage should be provided. Both the MCBs and WCBs are stored at a single facility. It is recommended to consider storage at multiple facilities (OC).

The culture broth is tested at the end of the manufacturing process for Mycoplasma, adventitious agents, mouse minute virus (MMV) and M. tuberculosis.

Process validation and evaluation

Three PPQ batches were manufactured at commercial scale. Results are presented for the in-process controls (IPCs) for the PPQ batches (cell viability and density, pH, glucose concentration, sterility/ mycoplasma/ adventitious agents/mouse minute virus/mycobacterium tuberculosis, and antigen content). The PPQ results for in-process and release data demonstrate that the manufacturing process consistently provides a Component A that meets its pre-defined acceptance criteria and quality attributes.

Process development

Process development studies were conducted to identify the impact of each process parameter on productivity (component A yield) and impurities in the production culture process. Based on these studies set points for the process parameters were established. The data provided are sufficient to support the upstream manufacturing and its process parameters settings.

Four different manufacturing processes are identified for component A: nonclinical, phase 1/2 clinical, phase 3 clinical, and commercial.

Characterisation

Six batches are used for the characterisation of Component A, including non-clinical, clinical and PPQ batches. The same characterisation data were also used to demonstrate and justify comparability between component A material of the different manufacturing processes. The primary sequence was determined by peptide mapping. Post-translational modifications demonstrated deamidation in the N-terminal peptide.**)**.

Binding affinity studies of component A to the human ACE2 receptor demonstrated that the RBD is present in component A.

In general, sufficient removal of process-related impurities is demonstrated.

Component B

Component B is manufactured in *E. coli*. The upstream process includes seed fermentation in Erlenmeyer flasks and production fermentation in a stainless steel fermenter, and harvest by two-step

centrifugation. The harvest is stored at or below -70 °C. The process steps are described in sufficient detail, however some questions are raised for clarification, a.o. holding times should be provided (**OC**). The downstream manufacturing process involves thawing the frozen harvest, cell disruption, isolation of inclusion bodies, chromatography steps, and UF/DF to concentrate component B protein to a target concentration and to change the buffer to the final composition. The UF/DF harvest is filtered and stored at -70 °C in disposable bags. The Applicant should provide additional details for the filters and Columns used in the manufacturing process of component B (OC). The Applicant should describe for each of the steps in what type of container the intermediate is collected (OC).

Component B is manufactured in E. coli bacteria in which a component B protein-expressing vector is inserted. A clear description of the history and preparation of a MCB and a WCB was provided. The MCB (MRN2201) and WCB (WRN2201) were characterised and tested in line with Ph. Eur. The date of manufacturing for both *E. coli* MCB and WCB should be provided (OC).

Batch information for 3 consecutive PPQ runs demonstrated consistency and all IPCs were met. The criticality assignment of the Process Parameters (PP) in the downstream process can be accepted.

Process development

Optimisation of process steps has been described. SDM Scaled down models (upstream and downstream) were used to optimise the process steps. These SDM were verified to the full-scale commercial process and based on this it can be accepted that the SDM is sufficiently representative of the commercial process. Also, the ranges of the PP are generally sufficiently supported, although some questions are raised for tightening or the criticality assignment (OC). The validation of chromatography resins lifetime, cleaning, and the leachables information should be provided (OC).

An overview of the Process modifications during development was provided. The provided comparability data consisted of batch analysis QC data of Component B of the different processes. These included appearance protein content, purity, endotoxin, sterility, HCD, HCP and sufficiently support comparability between the manufacturing processes.

Characterisation

Component B was characterised by peptide mapping and molecular weight and was confirmed to match the theoretical sequence and mass. These results sufficiently confirm the primary structure of component B. The characterisation studies for component B should be completed with the assessment of product-related impurities such as mass variants (aggregates, truncated forms, and/or other molecular variants) and charge variants (OC).

<u>RBD Nanoparticle</u>

Component A and B are thawed to start the manufacturing process of the RBD nanoparticle. The reaction solution is filtered and then UF/DF is used. The buffer is also changed to the final composition in the UF/DF step. After final filtration the substance is stored in disposable bags (≤ -70°C) until formulation. Further details of the steps should be included in the flow diagram (OC). The Applicant should describe in what type of container the drug substance is collected. (OC). Additional details are requested on the manufacturing process, a.o. scale, and information on filters and membranes (OC). An integrity testing of the membrane cassette before use should be implemented or its omission justified (OC). Additional acceptance criteria should be set for RBD particle (OC). The Applicant should provide further evidence of sufficient microbiological control of the manufacturing process. (OC)

Process performance qualification (PPQ) was performed on three consecutive batches for the RBD nanoparticle. An further explanation on the result of PPQ is requested.

Process development

Based on evaluation of the ultrafiltration/diafiltration (UF/DF) step for its capacity to remove non-self-assembled intermediate components (i.e. free component A and component B) and other impurities the Cut off size of the membrane was chosen. No free component B is detected in the final drug substance. However, the removal of Free Component A is far from complete.

The evaluation of the process using multivariate analysis included the PP and CQA and KPA (Key Process Attribute; i.e. process yield). Evidence should be provided that when the manufacturing process is running within the process ranges described in the Description of manufacturing process and process controls this will result in a product of the intended quality (OC). A QTPP should be defined (OC). A scaled down model (SDM) was used for evaluation of the PP. This was verified using a comparison of quality attributes of SDM and PPQ batches. These would support the suitability of the SDM. However, the Nanoparticle ratio data presented in different CTD sections are not in agreement. This should be clarified (OC). Furthermore, additional information is requested in support of the scale down model used in manufacturing process development and viral clearance studies (OC). Action limits and acceptance criteria for IPCs should be justified (OC). A history of all produced batches with the batch numbers, the manufacturing scale, their purpose and the manufacturing date should be provided, as well as the batch data (OC).

Sufficient understanding of the impact of process parameters on the percentage of free Component A should be demonstrated (part of MO).

RBD nanoparticle batches manufactured using the phase 1/2, phase 3 clinical and PPQ processes have been compared using data from characterisation and quality control testing. Generally the quality control data do not indicate major differences between the manufacturing processes. However, justification of the differences between particle size of PPQ batches and clinical batch is requested (OC). Also the polydispersity index should be provided (OC). The provided comparability data for the Nanoparticle are not sufficiently detailed. (OC) The comparability of the glycan structures of the nanoparticles is not demonstrated in sufficient detail. (OC)

Characterisation

Characterisation studies were conducted for RBD nanoparticle using materials from non-clinical, phase 1/2 and phase 3 clinical processes. The amino acid sequence for the RBD nanoparticle was confirmed with peptide mapping. Some differences in N-glycan structures and amounts were observed between (non-)clinical batches and the PPQ batches from the commercial process. These differences were also found for glycosylation pattern of component A for which it was requested to justify that the differences in glycosylation are not of clinical relevance (OC). Images are presented for the analysis of morphology and similar circular structures can be observed in all batches, confirming the presence of Nanoparticles.

Using Size exclusion chromatography (SEC) it was shown that both RBD nanoparticles and free component A are present in the clinical and PPQ batches. Since no free component B is observed and free Component A is observed (i.e. not part of a nanoparticle), the ratio between components A and B used for the self-assembly reaction are questioned (OC). Furthermore, it should be clarified if disintegration of the RBD nanoparticle might explain for the presence of free component A (OC).

The Applicant is requested to further elucidate the secondary and higher order structures of component A and component B and discuss the influence of the structure of component A and B on the self-assemblage of the RBD nanoparticle (OC). The characterisation studies should be completed with information on product-related impurities (e.g. fragments, deglycosylation, isomerisation, oxidation, deamidation among others) (OC). Since DS consists of free component A, an immunogenicity study was conducted in rabbits. Results demonstrated that both the RBD nanoparticle and free component A induced a high immune response, with the RBD nanoparticle inducing the highest immune response.

Due to the difference in immunogenicity between the RBD nanoparticle and free component A, it is essential that the level of RBD nanoparticle and free component A is controlled in Drug Substance (e.g. using SEC). (Part of MO). Further details should be provided on the in vivo immunogenicity study (OC).

The binding affinity of RBD nanoparticle to the receptor proteins human angiotensin-converting enzyme 2 (hACE2) or CR3022 confirms that the Receptor binding domain is present in the RBD nanoparticle.

Process-related impurities for the RBD nanoparticle are removed sufficiently.

Removal of product-related impurities throughout the manufacturing process has been studied by SEC analysis. This was performed after the self-assembly reaction, and after UF/DF. After the self-assembly reaction a large excess of component A is measured and no component B.

Materials used in the manufacture of component A and B are controlled by in-house or pharmacopoeia requirements. For some of the materials no information is provided on the composition. This is requested (OC). No material used in the manufacturing process of component A, B and the RBD nanoparticle is of biological origin, apart from benzonase which is derived from milk.

3.1.2.3. Specification, analytical procedures, reference standards, batch analysis, and container closure

Component A

The specifications of the component A include appearance, pH, protein content, purity, identity, endotoxin, sterility, residual host cell DNA and residual host cell protein.

The justifications of release specifications of Component A are provided. For the acceptance criterion for protein content an upper limit is requested (OC). Also, the acceptance criteria for Purity (both for the SDS-PAGE and CE-SDS tests) and for HCP should be clinically justified (OC).

(Note container closure and stability are discussed in the nanoparticle section).

Component B

The specifications of the component B include appearance, pH, protein content, purity, identity, endotoxin, sterility, residual host cell DNA and residual host cell protein.

The justifications of release specifications of Component B are provided. For protein content an upper limit is requested (OC). The acceptance criteria for Purity should be clinically justified (OC)

(Note container closure and stability are discussed in the nanoparticle section).

Nanoparticle

The specifications of the Drug Substance include appearance, pH, protein content and antigen content, identity, purity, sterility, particle size and PS-80 content.

The test for antigen content by ELISA serves as a potency test both for Drug Substance and Drug Product. This is acceptable as correlation between antigen content and immunogenicity has been shown in animal studies. The principle of the ELISA test is based on binding of the RBD to the ACE2 receptor. Both RBD nanoparticle and free component A contain the RBD and it is expected that they both will bind to the ACE2 receptor. It should be investigated if the ELISA has a different sensitivity for the RBD nanoparticle than for free component A (OC).

Due to the difference in immunogenicity between RBD nanoparticles and free component A, it is essential that their amounts are controlled at release (e.g. by Size Exclusion Chromatography), both in Drug Substance and Drug Product, which currently is not the case (MO). Also stability of the RBD

nanoparticle during storage has not been investigated. Currently it is not tested if during storage free component A and/or free component B are released from the RBD nanoparticle and shelf-life acceptance criteria should be set for RBD nanoparticles and Free component A (MO). A specification is established for mean particle size, but also a specification should be established for particle size distribution (OC). A release specification should be established for HCP at Drug Substance level. (OC). Furthermore, Shelf life acceptance criteria should be included for the stability-indicating CQAs (OC).

Assays and validation

The methods for appearance, pH, protein content, purity, identity, endotoxin and sterility, are used for component A, component B and RBD Nanoparticle. They are essentially the same, with some slight modifications. Component A and B are furthermore tested for host cell DNA and host cell proteins. RBD nanoparticles are tested for Antigen content, polysorbate-80 content and particle size.

For several non-compendial methods a more detailed description should be provided (e.g. SDS-PAGE, CE-SDS, antibodies used for detection of component A and component B, representativity and coverage of the commercial HCP kit used, inclusion of product specific HCP sample, number dilutions in the ELISA, translation of raw data in reportable result for the ELISA). For the Host Cell DNA test, type of commercial kit and supplier are requested) (All OCs). It should be investigated if the ELISA has a different sensitivity for the RBD nanoparticle than for free component A (OC). For validation of the methods summaries of validation results are provided. These are generally acceptable. However, for the Purity test (SDS-PAGE) additional parameters need to be validated (OC). For the validation of the identity test by dot blot for component B and for RBD nanoparticles further clarifications are asked. (OC). The starting residual HCP and DNA amount in the three component A PPQ batches before the HIC purification step should be provided (OC).

Reference standards have been established for Component A and Component B. For the RBD nanoparticle reference standard additional data are requested (OC). Also a protocol for future new Primary reference standards is requested (OC).

Batch analysis

Batch analysis results of RBD nanoparticles PPQ batches are provided. All acceptance criteria are met. Consistency of Particle size should be justified (OC). The justifications for the release specifications of the RBD Nanoparticle are provided. The acceptance criteria for some of the parameters are considered wide and should be tightened (OC).

Container closure

Components A and B and RBD Nanoparticle batches are filled in disposable ethylene vinyl acetate (EVA) copolymer bag and stored at $\leqslant$ - 70° C. The Applicant is expected to provide an extractables and leachables study results including the study set-up. (OC) The acceptance criteria regarding the proposed specification of the disposable EVA bags should be listed and the minimal dose of gamma irradiation should be clearly specified and a CoA provided (OC)

3.1.2.4. Stability

Component A

A preliminary shelf-life of 12 months at $\leqslant$ -70° C for component B is proposed and can be accepted, based on twelve months stability data for one phase 1/2 clinical batch, 9 months data for two Phase III clinical batches and 3 month data for 3 PPQ batches. The stability testing included appearance, pH, protein content and purity. Accelerated study data are available for 3 PPQ batches for 1 month.

RBD nanoparticle

The proposed preliminary shelf-life of 12 months at ⩽ -70° C for the RBD nanoparticle cannot be accepted. Supporting data is provided for 12 months for two phase 1/2 clinical batches. Long-term stability data are available for 2 Phase III clinical batches for 9 months and for 3 PPQ batches for 3 months. Batches are tested for appearance, pH, protein content, purity, antigen content, PS-80 content and particle size. Like in the release testing of the DS, the amount of RBD nanoparticle and free component A has not been tested in the stability studies. This should be added (part of MO). Comparability between clinical and commercial batches should be shown this should include extended characterisation assays, using suitable analytical methods including orthogonal methods (OC). Additional stability data are expected for the PPQ batches, including accelerated stability DS studies (OC).

3.1.3. Finished Medicinal Product

3.1.3.1. Description of the product and Pharmaceutical Development

Recombinant COVID-19 subunit nanoparticle (referred to as GBP510), contains recombinant nanoparticles displaying the receptor binding domain (RBD) of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The description of the DP should specify from which variant SARS-Cov-2 virus the vaccine is manufactured (OC). The antigen is composed of component A and component B, forming a self-assembled nanoparticle structure. GBP510 is colourless, clear, or slightly opalescent liquid (RBD 25 µg/0.25 mL) in a colourless and transparent 5 mL vial. It is to be accompanied with an adjuvant, AS03, which is to be mixed in 1:1 ratio at the time of use. The vaccine is provided as a multi-dose presentation. The volume after mixing one vial of antigen suspension (2.5 mL) with one vial of AS03 adjuvant emulsion (2.5 mL) corresponds to 10 doses of 0.5 mL vaccine.

The composition of the vaccine, before mixing with AS03 includes buffers (e.g., tromethamine), stabilizers (e.g., sucrose).

The adjuvant, AS03, is composed of squalene (10.69 milligrams), DL-α-tocopherol (11.86 milligrams) and polysorbate 80 (4.86 milligrams). Other Ingredients are: adjuvant vial: Sodium chloride, Disodium hydrogen phosphate, Potassium dihydrogen phosphate, Potassium chloride, Water for injections.

All excipients in the composition comply with the Ph. Eur. No novel excipients have been used. No overages are applied.

Drug product components were pre-selected for the formulation development of GBP510 based on the excipient compatibility study results. A summary of study results is requested (OC). The formulation of non-clinical, clinical and commercial batches should be provided (OC). Physiochemical and biochemical properties of the Drug Product have been investigated; a correlation has been shown between antigen content (as measured with ELISA) and immunogenicity (as shown in animal studies). Nanoparticle structures have been observed by transmission electron microscopy.

Different adjuvant candidates were evaluated including AS03, and Aluminium hydroxide. AS03 was chosen as the final adjuvant to be used in GBP510. AS03 is a well-known adjuvant manufactured by GSK and already approved as an adjuvant. Relevant information with regard to description and composition, specifications and testing and container closure were provided for AS03.

The compatibility of AS03 with GBP510 after mixing has been shown by studies on the physiochemical characteristics of GBP510 (e.g. pH, appearance, nanoparticle shape) after mixing with AS03. However, the effect of mixing on the RBD nanoparticle structural stability remains to be shown. This is raised as part of the major objection on control on RBD nanoparticle and component A content (MO). In addition the impact of mixing with AS03 on particle size should be studied (OC).

Differences between the non-clinical, clinical and commercial manufacturing process of GBP510 have been briefly described and concern amongst others differences in scale. An overview of non-clinical, clinical, development and commercial batches is lacking and should be provided, including batch analysis data, manufacturing sites, date of manufacture and a link to the Drug Substance batches that were used for Drug product manufacture (OC). Furthermore, it should be justified that the batches used in non-clinical studies are sufficiently representative (e.g. with respect to impurities) for the batches used in clinical studies (OC). Also additional data should be provided to support for the antigen content and *in vivo* immunogenicity correlation (OC). The information provided on Manufacture development is very limited and should be expanded with amongst others a definition of a QTPP, justification of the process changes, identification of the critical aspects of the manufacturing process and data supporting the ranges for critical and key process parameters, and the action limits and/or acceptance criteria proposed for in-process controls and in-process tests should be clearly justified (MO).

Precautions taken during manufacturing of the Drug Product to ensure sterility are appropriate. Container closure integrity is tested as an In-process Control test in the capping process instead of a release test, which is acceptable.

The container closure components (a 5mL multidose type I glass vial and a chlorobutyl stopper) comply with Ph. Eur. For demonstrating compatibility with GBP510, the Applicant refers to the stability studies. Extractables studies have been performed and results for leachables studies will be submitted once available, which is acceptable. Compatibility of the GBP510 mixed with AS03 in syringes during in-use storage should be shown (OC).

3.1.3.2. Manufacture of the product and process controls

GBP510 Drug Product is manufactured at SK Bioscience in Republic of Korea. Quality control testing of GBP510 Drug Product is performed both by SK Bioscience and Eurofins BioPharma, Ireland.

The GBP510 manufacturing process is a straightforward DP manufacturing process, i.e. preparation of the formulation buffer, thawing of the DS, formulation, sterile filtration, and sterile filtration and filling. Reprocessing is not performed. Too limited information is provided on process parameters. All critical process parameters (CPPs) and key process parameters (KPP) including their ranges should be provided (OC). Information on holding times should be provided, as also information on filter material and sterilisation conditions of the vials and stoppers (OCs). Also information regarding the calculation of the antigen content to be mixed with buffer should be given (OC).

In Process controls are generally considered adequate. In process controls on the formulation buffer are lacking and should be provided (OC). Furthermore some IPCs are indicated as PPQ only but are considered critical and should be included as routine IPCs (OC).

Process validation has been performed with three subsequent PPQ batches. One batch at low batch size and two batches at high batch size were manufactured. It should be explained how consistency in protein content between batches at low and high batch size is guaranteed (OC). A media fill test has been performed for the maximum batch size. No process hold time validation was performed. Additional information on hold time validation is requested (OC). Furthermore, filter validation studies should be provided, in line with EMA guideline on the sterilisation of the medicinal product active substance, excipient and final container (OC). The suppliers of vial, stopper and flip-off cap should be mentioned and CoA should be provided (OC).

3.1.3.3. Product specification, analytical procedures, batch analysis

The quality specifications of the DP include the appearance (also after mixing with adjuvant AS03); pH, protein content, identity, antigen content, endotoxin, sterility, particulates, osmolality, purity, and extractable volume after mixing with the AS03.

A release and shelf specification has not been established for RBD nanoparticles and free component A content. This is requested, as part of the Major Objection on control on RBD nanoparticle and free component A content (MO). A release and shelf specification should also be established for particle size and distribution (OC), and shelf-life acceptance criteria should be established for stability-indicating parameters (OC). The acceptance criteria for the specifications are in general acceptable. The acceptance criteria for protein content, antigen content and endotoxin are considered too wide and should be tightened, and the limits should be clinically justified (OC).

A declaration for the confirmation of no risk of nitrosamines in GBP510 by SK Bioscience is provided. This declaration is based on a risk evaluation, which should be provided (MO). The level of specific elemental impurities should be assessed following ICH Q3D (OC).

The description of analytical methods and validation thereof is in general acceptable. A few questions are raised (OCs). Reference standards are described in Module3.2.P.6. Batch analysis results of three drug product PPQ batches are provided and results comply with the release limits.

3.1.3.4. Stability of the product

The proposed shelf-life for the Drug Product is 12 months at 2-8°C. This is supported by long term stability studies for Phase I/II batches, Phase III batches and PPQ batches. Based on the presented data the proposed shelf-life cannot be granted as it is currently unclear if the batches used in the stability studies are representative for the commercial manufacturing process. Either the shelf-life storage period should be reduced or the lower limit at release for antigen content should be increased (MO). Additionally, stability data are requested on purity, particle size and particle size distribution (MO). Furthermore, analysis of RBD nanoparticle and component A content should be included in the stability studies. This is part of the Major Objection on control on RBD nanoparticle and component A content (MO).

It follows from in-use stability studies that after mixing with AS03, vials are chemically stable at room temperature for at least 24 hours. However, the testing package is not considered sufficient; data should be provided on purity, particle size and particle size distribution (OC). Furthermore, in order to control RBD nanoparticle stability, RBD nanoparticle content and component A content should be investigated in the in-use stability studies (raised as part of the MO on control on RBD and component A content).

3.1.3.5. Post approval change management protocol(s)

None

3.1.3.6. Adventitious agents

The evaluation of the risk of viral contamination includes characterisation of cell substrate for the absence of adventitious agents, control of starting materials, and testing component A culture broth for mycoplasma, adventitious agents, MMV and M. tuberculosis.

There are no animal-derived raw materials used in the manufacture of GBP510, except for benzonase, for which animal-derived components are used in its manufacture. The risk of TSE is considered to be negligible.

The selected model viruses that are used for the virus clearance studies consist of an enveloped RNA virus (MLV), an enveloped DNA virus (PRV), a non-enveloped RNA virus (Reo3) and a non-enveloped DNA virus (MMV). Only a summary of the virus clearance studies was provided and Virus clearance study reports should be submitted that provide details on how the virus clearance studies were conducted (OC). The virus reduction steps that were investigated were low pH inactivation, and Virus filtration.

3.1.3.7. GMO

Not applicable

3.1.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

Four major objections have been identified regarding Module 3 of the eCTD of SKYCovion. These pertain to the control of RBD nanoparticle content and free component A content at release, during storage and after mixing with adjuvant, the Drug Product control strategy, the Drug product shelf life and to the missing risk evaluation on nitrosamines.

In addition, notable other concerns have been identified.

The application is, therefore, not approvable from a quality point of view.

The major objection on control of RBD nanoparticle and free component A content pertains to the following;

Theoretically, each RBD nanoparticle consists of 20 trimers of component A and twelve pentamers of component B. The nanoparticle is formed by self-assembly after mixing component A, and component B. Component A consists of the Receptor Binding Domain (RBD) of the spike protein of the Wuhan strain. Component B is a naturally occurring bacterial enzyme that has been modified to assemble together with Component A into nanoparticles.

It has been shown in animal studies that the RBD nanoparticle elicits a higher antigen response than free component A by itself. Therefore, the presence of RBD in nanoparticles is relevant for vaccine efficacy. RBD nanoparticle and free component A content is not controlled at release or shelf-life. This is requested and raised as a Major Objection as this is considered an important CQA for vaccine efficacy. Furthermore, it is not clear if the RBD nanoparticle structure remains intact during the storage of the vaccine or after mixing with the adjuvant. This should be shown and this is requested as part of the Major Objection on control of RBD nanoparticle and component A content. Also, as part of this Major Objection, control of the process to ensure consistency concerning the RBD nanoparticle and free component A content should be demonstrated.

An excess of free component A is already measured after the self-assembly reaction, while no component B is measured, the ratio between components A and B used for the self-assembly reaction is questioned and this is raised as an Other Concern.

The Applicant should further justify that Component B, which is not covalently bound is considered a part of the active substance since it is not a target antigen and only a vehicle to present the antigen that is non-covalently bound.

The MO on DP shelf life was raised as a decline in antigen content is seen after 9 months storage at 2-8°C. Either the shelf-life storage period should be reduced or the lower limit at release for antigen content should be increased. Furthermore, the stability studies should be expanded with testing for particle size- and distribution, nanoparticles and component A content and purity.

A MO on the Drug Product control strategy was raised as this was not properly defined and justified; a QTPP should be established, critical aspects of the manufacturing process should be identified and data should be provided supporting the ranges for critical and key process parameters, and the action limits and/or acceptance criteria proposed for in-process controls and in-process tests should be clearly justified.

In general, the information provided in the quality dossier is considered too concise and therefore, many questions were raised as requests for additional information, justification or clarification;

During manufacturing development, several process changes were made to the manufacturing process of component A, component B, RBD nanoparticles and Drug Product, which are clearly described. Generally, the quality control data do not indicate major differences between the batches of the different manufacturing processes; however, for component A, Drug Substance and Drug Product, additional data or clarification are requested to confirm comparability between clinical batches and commercial batches.

The component A, component B and RBD nanoparticle manufacturing processed appear appropriately characterised. The operating ranges of the Process Parameters of the processes are appropriately established. However, several questions are raised for clarification. For the Drug Product manufacturing process, the information on critical aspects of the manufacturing process and establishment of the operating ranges is lacking and should be provided in order to demonstrate sufficient process understanding.

Process validation for component A, component B, Drug Substance and Drug Product demonstrate that the manufacturing process consistently provides Drug Substance and Drug Product that meet pre-defined acceptance criteria and quality attributes, and it can be concluded that the manufacturing process is under a sufficient state of control. However, additional questions are raised on missing information.

The specifications for components A, B, RBD nanoparticle and Drug Product are not considered adequate. A MO is raised on control of RBD nanoparticle and free component A content; tightening of acceptance criteria for several Quality attributes and clinical justification is requested, and additional control is requested, e.g. HCP control at the level of RBD nanoparticle. The ELISA test for antigen content is considered a surrogate potency test, and indeed a correlation between antigen content and immunogenicity has been demonstrated in animal tests. As the principle of the ELISA test is based on binding of the RBD to the ACE2 receptor, and as RBD is present both in the RBD nanoparticle, and in free component A, it is expected that the ELISA test does not discriminate between the RBD nanoparticles and free component A. In order to assure vaccine efficacy, additional control on RBD nanoparticle content and free component A content is essential, as requested in the Major Objection.

A shelf-life of 12 months at ≤ -70° C has been proposed for both component A, component B and RBD nanoparticle. As full comparability remains to be demonstrated between clinical batches that were used to substantiate the shelf life and PPQ batches, and as the stability testing package is not yet fully agreed upon, the shelf-life of 12 months at ≤ -70° C cannot be agreed yet for component A and RBD nanoparticles. For component B, the shelf life claim of 12 months at ≤ -70° C is agreed.

3.2. Non-clinical aspects

3.2.1. Introduction

3.2.2. Pharmacology

3.2.2.1. Primary pharmacodynamic studies

It should be noted that the dossier with respect to the primary pharmacology studies is considered of low quality. The following remarks are made:

- The study reports regarding the immunogenicity and challenge studies are very brief of nature and contain limited information (reflected in low quality figures, incorrect legends, etc.). In several cases, there are discrepancies between the study reports and Module 2.6 (e.g. with regard to challenge doses used), or (conclusions on) data are described but not shown.
- The neutralising capacity of anti-RBD antibodies is evaluated with PBNA and PRNT assays, but there is no clear trend in results between these two assays and between the preliminary and confirmed results from the PBNA assay. This subverts the reliability of the corresponding data. The Applicant should i) justify why the Applicant did not select a single method of measurement of neutralising antibodies, and ii) clarify the differences between the WT strains used (ancestral, D614G, Wuhan, Korea/KCDC03/2020, etc.) (OC).
- Several primary PD studies have been conducted with non-clinical batches of GBP510. No quality characterisation data was available for these batches. The Applicant should discuss whether the quality of these non-clinical batches is sufficiently representative of the clinical batches (see Quality MO/OC). In addition, the Applicant should i) describe the differences between the preclinical (AS03A) and the clinical (AS03) adjuvant batch by clarifying the meaning of the so-called "A" in the final formulation used in the non-clinical studies; and ii) discuss to what extent the peptide linker between the RBD and I53-50A may be degraded by enzymes. (OC)
- The design of the challenge studies are considered inadequate, and lack justification on e.g. the choice of antigen:adjuvant ratio and route and dose of viral challenge. Furthermore, only limited parameters were monitored post-challenge (e.g. no histopathology conducted in NHP studies), and therefore the clinical relevance of these studies is questioned (see OC-1 and 2).

Overall, these issues hampered the assessment of the non-clinical proof-of-concept, but at this time do not affect the overall benefit/risk assessment of this product, provided that the efficacy in the clinical dossier is adequately covered.

GBP510 is a recombinant protein which is based upon the SARS-CoV-2 spike protein, and includes the receptor binding motif which binds to the ACE-2 receptor. The receptor binding domain (RBD), originated from the parenteral D614G strain, is genetically fused to I53-50A via a small peptide linker, and forms component A. This is produced in Chinese Hamster Ovary (CHO) cells. I53-50B is produced in *E. Coli* and forms component B. Both components are mixed in a ~1:1 molar ratio, initiating self-assembly of the RBD nanoparticle (RBD-NP). Each nanoparticle displays 60 copies of the RBD antigen. The RBD-NP is considered the drug substance, and GBP510 is the drug product.

The immunogenicity and efficacy of non-clinical (RBD-NP) and clinical (GBP510) batches were evaluated in a series of studies conducted in multiple animal models, adjuvanted with either alum or AS03. AS03 (GlaxoSmithKline) is composed of α-tocopherol, squalene and polysorbate 80 in an oil-in-water emulsion, which is also used in the approved H1N1/2009 vaccine Pandemrix®. Since AS03 is used in the final clinical formulation, the assessment is mainly focussed on results obtained with this

adjuvant, and not on the results obtained with alum-adjuvanted formulations. Vaccine formulations were administered via the intramuscular route, following a two- or three-dose regimen.

The *in vitro* binding affinity of RBD-NP to the human ACE-2 receptor was determined via biolayer interferometry, however no study report or reference was provided. The provided figure in Module 2.6 is of poor quality, but seems to indicate that the affinity of RBD-NP to the hACE-2 receptor was approximately 2-fold higher compared to SARS-CoV-2 spike protein.

3.2.2.1.1. Immunogenicity studies following a two-dose regimen

In an initial immunogenicity study, female BALB/c mice were immunised with vehicle (saline or alum, it is not always clear which one is represented in the figures), non-adjuvanted RBD-NP at 0.2, 1 and 5 µg, RBD-NP at 0.2 and 5 µg + alum or RBD-NP at 0.2, 1 and 5 µg + AS03 on day 0 and day 21 (dosing volume of 50 µl). It should be noted that the antigen: adjuvant ratio in this study is different than the ratio used in the clinic (i.e. 25 µg GBP510 + 250 µL AS03). Serum samples were collected to assess the humoral immune response, based on RBD-specific total antibody titre on day 0, 14 and 35 (determined by ELISA) and antibody neutralising capacity on day 35 (determined by a PBNA using (D614G) SARS-CoV-2 S protein; and a PRNT using live wildtype (WT) SARS-CoV-2 virus (Korea/KCDC03/2020)). Splenocytes were harvested on day 35 to assess the cell-mediated immune response with an IFN-γ and IL-4 ELISpot assay.

In general, the humoral response (based on RBD-total IgG titres) was more pronounced on day 35 compared to day 14, supporting a 2-dose regimen. In addition, a 2-dose regimen with AS03-adjuvanted RBD-NP induced a stronger humoral response (based on RBD-total IgG titres and neutralising antibody titres) compared to alum-adjuvanted RBD-NP and non-adjuvanted RBD-NP. It is noted that the dose-response relationship was not clear for AS03-adjuvanted RBD-NP.

Immunisation with 5 µg RBD-NP adjuvanted with alum or AS03 led to moderate IFN-γ (Th1 cytokine) and IL-4 (Th2 cytokine) secretion by splenocytes compared to vehicle controls, thus a mixed Th1/Th2 response was induced. The induction of a Th2 response indicates a potential risk for Vaccine-Associated Enhanced Respiratory Disease (VAERD). However, the data was too limited to assess whether the mixed response was more pronounced towards IFN-gamma or towards IL-4. Therefore, no clear conclusion can be made with respect to the risk for VAERD.

In a subsequent study, female BALB/c mice were immunised twice with vehicle (saline), GBP510 at 5 µg + alum or GBP510 at 5 µg + AS03 on day 0 and day 21 (dosing volume of 100 µl). This GBP510 batch was also utilised in the phase I/II clinical trial. Serum samples were collected to assess the humoral immune response, based on RBD-specific total antibody titre on day 0, 14 and 35 (determined by ELISA) and antibody neutralising capacity on day 35 (determined by PBNA using (D614G) SARS-CoV-2 S protein).

In general, the humoral response was similar as observed with the non-clinical RBP-NP formulation (Study RSR510.04.03); the RBD-total IgG titres were higher on day 35 compared to day 14, and AS03-adjuvanted GBP510 induced a stronger humoral response (based on RBD-total IgG titres and neutralising antibody titres) compared to alum-adjuvanted GBP510.

3.2.2.1.2. Challenge studies following a two-dose regimen

Multiple studies were conducted in female K18-hACE2 transgenic (TG) mice and cynomolgus monkeys, to determine the adaptive immune response following a 2-dose regimen with either non-clinical or clinical batches, and protection after viral challenge.

A dose range finding study (Study RSR510.04.03) was conducted in K18-hACE2 TG mice to determine a suitable intranasal viral dose of WT SARS-CoV-2 virus (Korea/KCDC03/2020) for challenge. Based on the clinical observation and mortality during an 8-day observation period, the lowest tested dose of 5×10^4 PFU was selected for the subsequent study.

In an initial challenge study, female K18-hACE2 TG mice were immunised twice with vehicle (saline), RBD-NP at 0.2 and 5 µg + alum or RBD-NP at 0.2 and 5 µg + AS03 on day 0 and day 21 (dosing volume of 50 µl). It should be noted that the antigen:adjuvant ratio in this study is different than the ratio used in the clinic (i.e. 25 µg GBP510 + 250 µL AS03). Serum samples were collected to assess the humoral immune response, based on RBD-specific total antibody titre on day 0, 14 and 35 (determined by ELISA) and the antibody neutralising capacity on day 35 (determined by a PBNA using (D614G) SARS-CoV-2 S protein and a PRNT using live WT SARS-CoV-2 virus (Korea/KCDC03/2020)). On day 42 (i.e. 21 days after second injection), the animals were intranasally challenged with 5×10^4 PFU of WT SARS-CoV-2 (Korea/KCDC03/2020). During an 11-day observation period, the animals were monitored for body weight, body temperature and survival rate. Additionally, 5 days post-challenge, the viral load in the lungs was determined by a plaque assay in 3/10 animals, and histopathology scores were evaluated. It is regretful that data of the lung viral load are not available for all animals to be able to apply statistics and better interpret the results.

Regarding the RBD-specific total IgG titres, generally similar trends were observed as in the initial immunogenicity study conducted in BALB/c mice (Study RSR510.04.03); the levels were higher on day 35 compared to day 14, and AS03-adjuvanted RBD-NP induced higher levels compared to alum-adjuvanted RBD-NP (based on RBD-total IgG titres and neutralising antibody titres). Overall, the humoral response in K18-hACE2 TG mice was lower compared to the response in the BALB/c mice. This could be the consequence of the difference in murine strain, as Balb/c mice tend to produce a stronger humoral response than C57BL/6 mice.

After the intranasal viral challenge, 100% mortality was observed after 9-10 days for vehicle control animals. 5-6 days post-challenge, these animals displayed significant weight loss (of up to 15%), decreased body temperature (by >10°C), high lung viral loads ($\geq 10^5$ PFU), and cellular infiltration and inflammation within the lung. Both alum- and AS03-adjuvanted RBD-NP immunised animals were protected from these clinical signs, and no mortality was observed in these animals. Additionally, lung viral load was significantly reduced to undetectable levels at day 5 post-challenge. Finally, lung histopathology demonstrated reduced inflammation, oedema and capillary dilatation in both alum- and AS03-adjuvanted RBD-NP immunised animals, but this effect was more pronounced in AS03-adjuvanted animals (albeit not significantly lower). Additionally, there was no evidence of an exacerbation of lung injury and this indicates that an antibody-dependent enhancement of disease (ADE) is not to be expected with the studied dosing and antigen: adjuvant regimen.

In a subsequent study, female K18-hACE2 TG mice were immunised twice with vehicle (saline), GBP510 at 5 µg + alum or GBP510 at 5 µg + AS03 on day 0 and day 21 (dosing volume of 100 µl). Serum samples were collected to assess the humoral immune response, based on RBD-specific total antibody titre on day 0, 14 and 35 (determined by ELISA) and antibody neutralising capacity on day 35 against the WT (D614G), alpha (B.1.1.7), beta (B.1.351) and gamma (P.1) variant virus (determined by PBNA). On day 42, the animals were intranasally challenged with 1×10^4 PFU of either WT (Korea/KCDC03/2020), alpha (Korea/KDCDCA51463/2021; B.1.1.7) or beta (Korea/KDCDC55905/2021; B.1.351) strains of SARS-CoV-2. During a 12-day observation period, the animals were monitored for body weight, body temperature and survival rate, but no viral load or lung histopathology was determined. The data regarding the protective effect of vaccination against challenge with variant strains are therefore limited.

It should be noted that there are some discrepancies between the study report and written and tabulated pharmacology summaries. In the study report and pharmacology summaries both day 42 and 49 are mentioned for the timing of the challenge. In the pharmacology written summary, both $1x10^4$ and $5x10^4$ PFU are stated as the amount of virus used for the challenge, but in the pharmacology tabulated summary and study report $1x10^4$ PFU is mentioned. In case $1x10^4$ PFU was used, the Applicant provided no justification for this choice, since the previous study in female K18-hACE2 TG mice (RSR510.04.03) identified a 5-fold higher challenge dose (lowest dose tested in the dose-range finding study) as most suitable.

Regarding the RBD-specific total IgG titres, similar trends were observed as in the immunogenicity study in BALB/c mice (Study RSR510.04.03); the levels were higher on day 35 compared to day 14, and AS03-adjuvanted GBP510 induced higher levels compared to alum-adjuvanted GBP510.

Animals immunised with either alum- or AS03-adjuvanted GBP510 produced antibodies with cross-reactivity against WT and variant forms of SARS-CoV-2 pseudovirus, albeit notably less effective for the variants. It should be noted that the results of the neutralising capacity are preliminary of nature (generated from pooled serum samples), and the interpretation of these data is difficult. However, they are mostly superseded by the data of the subsequent intranasal challenge.

After the intranasal viral challenge with different strains, 100%, 100% and 66% mortality was observed after 10 days for vehicle control animals challenged with the WT, alpha or beta strain, respectively. These animals displayed significant weight loss and decreased body temperature. In contrast, these clinical signs were not observed in AS03-adjuvanted GBP510 immunised animals, resulting in a 100% survival rate.

In a challenge study, adult male and female cynomolgus monkeys were immunised twice with vehicle (saline), GBP510 at 25 µg + alum or GBP510 at 25 µg + AS03 on day 0 and day 21. This is equal to the dose used in humans. Serum samples were collected to assess the humoral immune response based on RBD-specific total antibody titre on day 21 and 42 (determined by ELISA) and antibody neutralising capacity on day 21 (data not provided) and 42 with a PBNA against the WT (D614G), beta (B.1.351), delta and gamma variant (P.1) virus or with a PRNT for WT (Wuhan), alpha (B.1.1.7), beta (B.1.351) and gamma variant (P.1) virus. On day 42, peripheral blood mononuclear cells (PBMCs) were isolated to evaluate the cell-mediated immune response via an IFN-γ and IL-4 ELISpot assay. On day 49, the animals were challenged with a total of $2.6x10^6$ $TCID_{50}$ (~$1.82x10^6$ PFU, reference: https://www.atcc.org/support/technical-support/faqs/converting-tcid-50-to-plaque-forming-units-pfu) of WT SARS-CoV-2 (Korea/KCDC03/2020) intranasally (0.5 mL), intratracheally (4 mL), ocularly (0.25 mL/eye) and orally (5 mL). During a 7-day observation period, nose and throat swabs were collected on multiple days. However, no viral load in the lower respiratory tract was determined, nor lung histopathology was performed. The study report states that clinical signs were monitored after the challenge, however these data are not reported. It is therefore unknown if the challenge was sufficient to induce (lung) disease in this animal model and thus to determine whether the vaccine can sufficiently protect against COVID disease.

According to the Applicant, RBD-specific total IgG titre was increased from day 21 and had further increased by day 42, and in contrast to the immunogenicity studies in BALB/c and K18-hACE2 TG mice, alum-adjuvanted GBP510 induced higher mean levels compared to AS03-adjuvanted GBP510. In addition, the neutralising capacity was highest towards the WT strain and cross reactivity towards the variant strains was also noted, albeit notably less effective. However, no data on day 21 were provided by the Applicant. Furthermore, it is noted that there is high variability between the preliminary PBNA, confirmed PBNA and PRNT data, demonstrating different magnitudes of change and different trends. In Module 2.6, the Applicant states that "both the PBNA and PRNT are not formally validated and on occasion failed to demonstrate a consistent dose-dependent increase in neutralising antibody titre, but

that there was good agreement between both assays (PRNT and PBNA, whether preliminary or definitive) whereby the titres for AS03-adjuvanted RBD-NP>>RBD-NP+alum>RBD-NP>vehicle". However, this 'good agreement' appears not the case when assessing the different strains, and it is not clear which data are reliable. Therefore, final conclusions on the efficacy of the vaccine against virus variants cannot be drawn.

Immunisation with GBP510 adjuvanted with alum or AS03 led to moderate IFN-γ and IL-4 secretion by PBMCs compared to vehicle controls, thus a mixed Th1/Th2 response was induced. The data showed high variability and is considered too limited to assess whether the mixed response was more pronounced towards IFN-gamma or towards IL-4. Therefore, no clear conclusion can be made with respect to the risk for VAERD.

After the viral challenge, virus was detected in both nose and throat samples for 5 days in the vehicle group. In contrast, only low levels were detected during the first 2 days in the AS03-adjuvanted GBP510 group, and no virus was detected in the alum-adjuvanted group. This indicates that both formulations were sufficient to suppress viral replication in the upper respiratory tract, but overall, alum-adjuvanted GBP510 performed slightly better in the cynomolgus monkey.

3.2.2.1.3. Studies following a three-dose regimen (currently out of scope)

A series of immunogenicity and challenge studies have been conducted with various presentations of the RBD-NP (derived from either WT or beta strain of SARS-CoV-2), formulated with AS03, in order to compare the efficacy of a two-dose vs three-dose regimen. The activity of the different RBD-NP formulations was evaluated against a series of VoCs.

In an initial immunogenicity study, female BALB/c mice were immunised with vehicle (NP buffer) or with AS03 -adjuvanted RBD-NP at 0.2 and 5 µg. It should be noted that the antigen: adjuvant ratio in this study is different than the ratio used in the clinic (25 µg GBP510 + AS03). The immunogenicity response was evaluated following two doses of RBD-NP-WT (Korea/KCDC03/2020) on day 0 and 21 versus three doses of RBD-NP where the third dose administered on day 42 was either RBD-NP-WT (Korea/KCDC03/2020), RBD-NP-Beta (Korea/KDCA55905/2021; B.1.351) or a bivalent vaccine (1:1 mixture of WT and Beta). Serum samples were collected to assess the humoral immune response based on RBD-specific total antibody titre on day 14, 35 and 56 (determined by ELISA) and antibody neutralising capacity on day 56 against the WT (D614G), beta (B.1.351), delta (B.1.617.2), gamma (P.1) and omicron variant (B.1.1.529) virus (determined by PBNA). Splenocytes were harvested on day 56 to assess the cell-mediated immune response based on an IFN-γ and IL-4 ELISpot assay.

The humoral immune response, based on RBD-total IgG titres, was dependent on the number of doses. In line with the previous immunogenicity results following a two-dose regimen, the response was more pronounced on day 35 compared to day 14. However, at day 56, the titres were slightly lower compared to day 35. A third dose given on day 42, independent of the strain used in the formulation, resulted in similar or slightly higher levels on day 56 compared to day 35. The neutralising activity against the beta and gamma variants was similar to that observed for the WT strain, while the activity against the delta and omicron strain was clearly lower. The activity across all strains increased after a third dose. Whether the slight increases in total RBD-specific titres and neutralising activity with a three-dose regimen would have a considerable effect on the efficacy of the vaccine was determined in subsequent challenge studies (see below).

In line with the previous immunogenicity results following a two-dose regimen, immunisation with AS03-adjuvanted RBD-NP led to moderate IFN-γ and IL-4 secretion in splenocytes compared to vehicle controls. The secretion increased after a third dose, but there was a high variability, which hampers the possibility to draw firm conclusions regarding this third dose. The Applicant states that the cell-

mediated immune response data indicate a more Th1 dominant response, suggesting a reduced potential for VAERD. However, the absolute count data (spots/well) was not provided, and therefore this statement could not be verified.

In a subsequent challenge study, female K18-hACE2 TG mice were immunised with vehicle (saline) or with AS03-adjuvanted RBD-NP at 5 µg. It should be noted that the antigen: adjuvant ratio in this study is different than the ratio used in the clinic (25 µg GBP510 + AS03). The clinical and immune responses were evaluated following two doses of RBD-NP(-WT) on day 0 and 21 versus three doses of RBD-NP where the third dose administered on day 42 was either with RBD-NP-WT, RBD-NP-Beta or a bivalent vaccine (1:1 mixture of WT and Beta). Serum samples were collected to assess the humoral immune response based on RBD-specific total antibody titre on day 14, 35 and 56 (determined by ELISA) and the antibody neutralising capacity on day 56 against the WT (Korea/KCDC03/2020), alpha variant (B.1.1.7), beta variant (B.1.351), delta variant (B.1.617.2) and gamma variant (P.1) virus (determined by a cytopathic effect-based neutralisation assay). On day 63, the animals were intranasally challenged with 1×10^4 PFU of either WT, alpha (B1.1.1.7), beta (B.1.351), gamma (P.1) or delta (B.1.617.2) strains of SARS-CoV-2. The Applicant provided no justification for this challenge dose, while the previous study in female K18-hACE2 TG mice (RSR510.04.03) identified a 5-fold higher challenge dose (lowest dose tested in the dose-range finding study) as most suitable. On day 5 post-challenge, a subgroup of animals was euthanised to assess lung viral load (via plaque assay and RT-qPCR), histopathology and cytokine levels (TNF-α, IL-6 and MCP-1) within the lung tissue and bronchoalveolar lavage fluid (BALF). The remaining animals were monitored for body weight and temperature, clinical signs, lung viral load (via RT-qPCR) and survival rate during a 14-day observation period post-challenge.

The humoral immune response in K18-hACE2 TG mice followed a similar trend as in the previous study in BALB/c mice (Study RSR510.04.06). The total antibody response against SARS-CoV-2 RBD increased over time with the number of immunisations, irrespective of the strain used in the formulation. The neutralising activity against the WT strain and VoCs also further increased after a third injection. It should be noted that the legend provided by the figure in the study report is not correct.

After the intranasal viral challenge with different strains, 100% mortality was observed after 6-10 days for vehicle control animals challenged with the WT, alpha and beta strain. 90% and 80% mortality was observed after 6-11 days for vehicle control animals challenged with the gamma and delta strain, respectively. These animals displayed significant weight loss and decreased body temperature. In contrast, these clinical signs were not observed in immunised groups, resulting in a 100% survival rate. Five days post-challenge, immunised animals showed reduced viral load, reduced production of inflammatory cytokines (TNF-α, IL-6 and MCP-1) and lower histopathological scores were observed, with no notable difference between the two- or three-dose regimen, nor a difference in the used strain in the formulation or challenge. On day 14 post-challenge, similar results were observed since lower viral loads were observed in all immunised animals, with no difference between a two- or three-dose regimen, nor a difference in the used strain in the formulation or challenge. It should be noted that the viral load in vehicle treated animals was already determined on day 7 post-challenge, and not on day 14. It is not clear why the viral load in vaccinated animals was not determined at the same time point, as this would allow for a more relevant comparison. In addition, it is unclear why at 5 days post-challenge with the delta or WT strain, none or very low viral load was detected , whereas at 14 days post-challenge with the delta or WT strain the viral load appears higher. Since only limited challenge data are provided, the Applicant is asked to discuss the relevance of the study design and results for evaluation of vaccine efficacy, taking into account (I) the comparison of day 7 data from vehicle controls with day 14 data from vaccinated animals , (II) the differences in viral load after 5 and 14 days in immunised animals, (III) the differences in viral load after 5 days between this study and the

results obtained in female K18-hACE2 TG mice in the previous challenge study (Study RSR510.04.03, Figure 2.3.3.1.2), and (IV) the Applicant should also clarify if in this last study the same technique was used to determine the viral load. If not, the comparability between the results should be discussed. Finally, the Applicant is asked to confirm that the provided results are correct with regard to the mentioned timepoints, since the Applicant refers to results of 5 days post challenge for Figure 2.3.4.2.3 ("all RBD-NP immunised mice exhibited significantly lower viral loads (within the lung) at 5 dpi when compared to the corresponding vehicle treated controls"), but the legend indicates 7 and 14 days post-challenge (OC).

In a final challenge study, adult rhesus monkeys (sex is not mentioned in study report) were immunised with vehicle (saline) or AS03-adjuvanted RBD-NP at 25 µg. This is equal to the dose and antigen: adjuvant ratio as used in humans. The response was evaluated following two doses of RBD-NP-WT on day 0 and 28 versus 3 doses of RBD-NP where the third dose (administered on day 56) was either RBD-NP-WT or RBD-NP-Beta.

Serum samples were collected to assess the humoral immune response based on WT, beta and delta RBD-specific IgG titre on day 0, 14, 28, 42, 56, 70 and 77 (determined by ELISA) and antibody neutralising capacity on day 14, 28, 42, 56 and 70 with a PBNA against the WT (Wuhan/WIV04/2019), beta (B.1.351), delta (B.1.617.2) and omicron variant (B.1.1.529) virus. On day 70, PBMCs were isolated to determine the cell-mediated immune response via an IFN-γ ELISpot assay. On day 77, the animals were intranasally and intratracheally challenged with 5×10^5 $TCID_{50}$ (~$3.5x10^5$ PFU, reference: https://www.atcc.org/support/technical-support/faqs/converting-tcid-50-to-plaque-forming-units-pfu) of the delta (B.1.617.2) variant of SARS-CoV-2. It is unclear how this challenge dose was chosen, since the Applicant refers to a study in rhesus monkeys (Munster et al., 2020) where a challenge dose of $4x10^5$ $TCID_{50}$ was used, and previously referred to another study in rhesus monkeys (Van Doremalen et al., 2020) where a challenge dose of $2.6x10^6$ $TCID_{50}$ was used. During a 10-day observation period, the viral load in the upper (via nasal swabs) and lower (via BALF) respiratory tract was assessed for each group on multiples days, using a subgenomic RNA assay. The study reports states that clinical signs were monitored after the challenge, however these data are not reported. Additionally, no lung histopathology was performed. It is therefore unknown whether the challenge was sufficient to induce COVID-related (lung) disease in this animal model, similar to the challenge study following a two-dose regimen in cynomolgus monkeys (Study RSR510.04.04). Therefore, the Applicant is asked to justify the design of the challenge studies (including challenge dose, route of administration, location of sampling, monitored pre- and post-challenge parameters/clinical signs) in the light of natural SARS-CoV-2 infection and the pathology observed in humans, and subsequently discuss the clinical relevance of the studies in NHPs (OC).

The humoral immune response, based on WT-, beta-, or delta-specific RBD IgG titres, was dependent on the number of doses. In line with the previous immunogenicity results following a 2-dose regimen (Study RSR510.04.03 and RSR510.04.04), the response was more pronounced after the second dose compared to the first dose and maximum titres were reached around day 42. A third dose given on day 56, independent on the strain used in the formulation, resulted in even higher levels of all specific RBD IgGs, demonstrating the added value of a third injection. The neutralising activity of the anti-RBD antibodies against WT, beta, delta and omicron strains of SARS-CoV-2 increased following the third injection, with a slightly more pronounced effect when RBD-NP-WT was used compared to RBD-NP-Beta. Interestingly, the neutralising antibody levels against the VoC were similar to WT at day 70 following a third dose, while after only two doses mean titres against WT virus were considerably higher than those against the VoC viruses.

As expected, IFN-y secretion in PMBCs was higher on day 70 after three doses compared to 2 doses, irrespective of the strain used in the formulation. Unfortunately, IL-4 secretion was not measured in this study, so no statement can be made on the potential risk for VAERD.

After the viral challenge, virus was detected in both the upper and lower respiratory tract for 10 days in vehicle immunised animals. Viral clearance was more effective after the third dose compared to only two doses. No difference was observed between the RBD-NP-WT or RBD-NP-Beta groups.

3.2.2.2. Secondary pharmacodynamic studies

In accordance with the WHO guideline on adjuvanted vaccines (2013), the absence of dedicated secondary PD studies can be endorsed.

3.2.2.3. Safety pharmacology programme

The Applicant has performed 7 GLP-compliant safety PD studies, of which 4 were conducted with AS03-adjuvanted GBP510 (30 µg, antigen and adjuvant mixed in 1:1 ratio, formulation GBP519-001A). The other studies (conducted with other adjuvants) are at most considered supportive of the safety of GBP510. (Non-)clinical data from other vaccines containing AS03 and non-clinical repeat-dose toxicity data with the current vaccine would be considered sufficient to support the safety of the vaccine. No stand-alone safety PD studies would be needed. However, the Applicant has provided a rationale for performing such safety PD studies next to repeat-dose toxicity studies, especially with respect to cardiovascular safety. In line with the 3R principles, studies were only performed in males. This is considered acceptable.

In the safety PD studies, the Applicant examined the effect of (AS03-)adjuvanted GBP510 as single IM injection on the central nervous, respiratory and cardiovascular systems in rat and dog. No vaccine-related effects were found in general behaviour and on the functionality of the CNS (rat) and cardiovascular system (dog). In contrast, the vaccine induced a temporary rise in body temperature (which was also observed in the repeat-dose toxicity studies), tidal volume and minute volume in rats, approximately 4-6h post-dose. At 48h post-dose, these values had returned to baseline. Although not further discussed by the Applicant, it is very likely that these responses in vital systems are related to an (adequate) immunological response to the adjuvanted vaccine (i.e. PD-related). These effects are therefore also likely to occur in vaccinated humans, but are not expected to pose a serious clinical risk.

It was noted that all safety PD studies have been conducted with non-clinical batches of GBP510. No quality characterisation data was available for these batches. The Applicant should discuss whether the quality of these non-clinical batches is sufficiently representative of the clinical batches (see Quality MO/OC).

3.2.2.4. Pharmacodynamic drug interactions

No dedicated non-clinical pharmacodynamic drug interaction studies were performed. This is endorsed.

3.2.3. Pharmacokinetics

According to WHO guidelines on non-clinical evaluation of vaccines (WHO 2005) and vaccine adjuvants and adjuvanted vaccines (WHO 2013), traditional absorption, distribution, metabolism, and excretion (ADME) evaluations are not generally needed for vaccines. The safety concerns associated with vaccines are generally not related to the pharmacokinetics but are related to the potential induction of immune response. In addition, AS03 is not a novel adjuvant and therefore, biodistribution studies are not considered necessary. The absence of pharmacokinetic studies is agreed with.

3.2.4. Toxicology

3.2.4.1. Single dose toxicity

The absence of single dose toxicity studies is acceptable.

3.2.4.2. Repeat dose toxicity

A GLP-compliant repeated dose toxicity study was conducted in Sprague-Dawley Rats (15/sex/group), which received 2 intramuscular injections (Day 1 and Day 15) with saline, or GBP510 at 30 µg adjuvanted with either Alum+CpG 1018 or AS03 followed by a 4 week recovery period. The dose is slightly higher than the intended clinical dose (25 µg GBP510, with AS03). A non-adjuvanted GBP510 group was not included, which is considered acceptable since AS03 is a well-known adjuvant. The study was performed using non-clinical batches. No quality characterisation data was available for these batches. The Applicant should discuss whether the quality of these non-clinical batches is sufficiently representative of the clinical batches. See quality MO and OC regarding the manufacture and pharmaceutical development of the drug product.

The assessment below mainly focuses on observations made in the GBP510 and GBP510 + AS03 group, which are most relevant for the clinic. The other groups (conducted with other adjuvants) are at most considered supportive of the safety of GBP510. Levels of anti-RBD, anti-component B and anti-I53-50A-OG IgG antibodies were increased after 1 dose (measured at Day 14), but even more after 2 administrations (measured at Day 29) of adjuvanted GBP510. At Day 43, antibody levels were slightly lower than at Day 29.

The vaccine resulted in effects on clinical pathology parameters and histopathology that are consistent with immune stimulation following administration of a vaccine, amongst others increased body temperature at 6 and 24 hours (but no longer at 48h) after administration, altered red blood cell parameters, increased white blood cell count, increased fibrinogen and prothrombin.

In the AS03-adjuvanted females, urine volume was significantly decreased, but no histopathological changes were observed in kidney or bladder and no changes were observed in other urinalysis parameters. In addition, in the 3-dose study (see below), an increase in urine volume was observed in females. The finding is therefore considered not to be treatment-related.

A significant increase in spleen weight was noted, associated with minimal to mild extramedullary haematopoiesis and increased cellularity in white pulp. Increased liver weight at the end of the treatment period was also associated with minimal to severe extramedullary haematopoiesis and minimal to mild microvesicular fatty changes. In addition, reduced thymus weight was observed. These changes are likely related to a vaccine-induced immune response.

Further changes were not considered vaccine-related because they were within historical range and not associated with histopathological findings. This included decreased relative/absolute pituitary gland and absolute heart weights in males and increased relative/absolute lung weight in females.

Local effects at the injection site included moderate to severe granulomatous inflammation, minimal to mild myofiber necrosis, minimal to moderate myofiber atrophy, mild to massive granulomatous inflammation outside the skeletal muscle and/or mild to severe purulent exudate in the granulomatous inflammation, as well as increased cellularity of lymphocyte and/or plasma cell in the axillary and iliac lymph nodes. In addition, minimal to moderate granulomatous inflammation and mild to massive inflammatory cell infiltrate was observed in the perineural connective tissue of the peripheral nerve. This was considered to be a non-adverse immunological reaction.

In general, similar effects were observed in the Alum+CpG-adjuvanted group, however, most effects were slightly stronger and/or more persisting in the Alum+CpG adjuvanted group.

At the end of the recovery period, all effects were resolved or reduced in incidence and/or severity.

In a second GLP-compliant study with a similar set-up, the potential toxicity of GBP510 vaccine (30 µg) adjuvanted with MF59 (1:1 ratio) or Aluminium hydroxide and administered on Day 1 and Day 15 was evaluated. Since GBP510 was not administered without adjuvant, the effects of the antigen itself and the adjuvant cannot be separated and therefore, the results of this study are considered only as supportive. In general, the observed effects were similar as for the previous study, although body temperature did not increase to levels above 39°C in the MF59-adjuvanted group.

Another GLP-compliant repeated dose toxicity study (Study No. 20-RR-0935) was conducted in Sprague-Dawley Rats (15/sex/group), this time receiving 3 intramuscular injections (Day 1, Day 15 and Day 29) with saline, or GBP510 at 30 µg adjuvanted with either Alum+CpG 1018 or AS03, followed by a 4 week recovery period. Also this study was performed using non-clinical batches. No quality characterisation data was available for these batches. The Applicant should discuss whether the quality of these non-clinical batches is sufficiently representative of the clinical batches. See quality MO and OC regarding the manufacture and pharmaceutical development of the drug product.

The assessment below mainly focuses on observations made in the GBP510 and GBP510 + AS03 group, which are most relevant for the clinic. The other groups (conducted with other adjuvants) are at most considered supportive of the safety of GBP510.

In general, findings were similar to those observed in the 2-dose study (see assessment of Study 20-RR-0828), differences with this study included a significantly increased body weight gain in females (although within historical control range) and an increased urine volume in females. Since both effects are only observed in females, opposite to the effects observed in the 2-dose studies, as well as reversible, they are not considered adverse and/or treatment-related.

All observed effects were partially or fully reversible by the end of the recovery period.

Levels of IgG antibodies for RBD, component B and I53-50A-OG showed a small increase after the first dose, and a further increase after the second dose (10-11 times higher on Day 28 compared to Day14). Although antibodies for component B increased slightly further after the third dose (2.6 times higher on Day 43 compared to Day 28), antibodies for RBD and I53-50A-OG were slightly lower after a third dose (0.7 x). On Day 57 (end of the recovery period) all antibodies were further reduced (0.5-0.8x versus Day 43). Value of the third dose is described and assessed in the Pharmacology section of this AR.

Also for the 3-dose set-up, a similar study was performed with GBP510 vaccine adjuvanted with MF59 or Aluminium hydroxide. Results were comparable to the other studies and are considered only supportive and are therefore not further described.

3.2.4.3. Genotoxicity and carcinogenicity

The absence of genotoxicity and carcinogenicity studies is accepted. Not required for vaccines.

3.2.4.4. Reproductive and developmental toxicity

A reproductive and developmental toxicity study was conducted in female SD rats to assess the effect of non-adjuvanted GBP510, alum-adjuvanted GBP510 and AS03-adjuvanted GBP510 (GBP510-006A) on maternal toxicity, fertility and embryo-foetal and pre- and post-natal development. A negative control (saline) as well as a vehicle control (Alum) were included.

In the caesarean section group, dams (25/group) were injected intramuscularly into the left and right hindlimb at 4 weeks and 2 weeks before pairing (i.e. on Day 1 and 15), and on gestation day (GD) 8 and 15 (thus in total 4 times). These animals were used for evaluation of embryo-foetal development. In the natural delivery group, dams (25/group) received an additional injection on lactation day (LD) 7 (thus in total 5 administrations). These animals were used for evaluation of pre- and postnatal development.

The dose level used was 30 µg GBP510 (0.5 ml), except for the AS03-adjuvanted GBP510 group, which received only 12 µg (0.2 ml), which is lower than the intended clinical dose (25 µg). The Applicant should justify this lower dose, since the WHO guidelines on non-clinical evaluation of vaccines indicates that 'the highest dose (in absolute terms) to be used in the proposed clinical trial should be evaluated in the animal model'. The fact that 30 µg in 0.5 ml is used for the other adjuvant groups as well as for the AS03-adjuvanted GBP510 group in the repeated dose toxicity studies shows that limitation due to volume is not an issue. In addition, it is not clear why an Alum vehicle control group is included, but not an AS03 vehicle control group, considering the fact that AS03 is the adjuvant of choice in the clinical studies. Also this should be justified.

In the caesarean section group, no abnormal clinical signs were observed. There was a tendency towards a lower number of pregnancies in the AS03-adjuvanted GBP510 group (20 versus 23 in the control group), however, this was not observed in the natural delivery group and is therefore not considered treatment-related.

No differences were observed in number of corpora lutea, number of implantations, resorptions, pre- or post-implantation loss or number of dead and live foetuses.

In the non-adjuvanted GBP510 group there was a tendency towards an increased incidence of foetal external findings (48% of litters compared to 28.6% in negative control). The main difference observed was a small placenta. This was not observed in the adjuvanted GBP510 groups. In addition, the incidence was within the historical control range. Furthermore, in several other animals from this group, a large placenta was observed (incidence similar to control group). Therefore, this finding is not considered treatment-related.

No skeletal malformations were observed in the non-adjuvanted GBP510 or AS03-adjuvanted GBP510 groups.

There was a tendency towards an increase in the litter incidence of skeletal retardations (mainly Dumbbell ossification of thoracic centrum) in the non-adjuvanted GBP510 or AS03-adjuvanted GBP510 groups (30.4 and 20% of the litters, respectively, compared to 9.5% in negative control litters), as well as in the vehicle control group. However, these incidences were within the historical control range.

No increase in skeletal or visceral variations was observed in the non-adjuvanted GBP510 or AS03-adjuvanted GBP510 groups, although it was noted that 2 animals (of 2 different litters) of the GBP510+AS03 group had a convoluted ureter, whereas this was not observed in any foetus from the other groups.

In the natural delivery subgroup, beside local changes at the injection site, no clinical signs were observed in the dams or pups. No adverse effects were observed on number of pregnancies, pre- and post-natal survival, growth or development of the offspring up to Day 21 of age.

Evaluation of the immune response in dams (at GD21 and LD21), foetuses from the caesarean section subgroup (at GD21) and pups from the natural delivery subgroup (at PND 21) indicates that anti-RBD IgG antibodies can be transferred from F0 dams to F1 offspring during gestation. The amount of anti-RBD IgG antibodies in pups is further increased during lactation, showing that also antibody transfer via milk occurs.

The absence of juvenile studies is agreed.

3.2.4.5. Tolerance

The absence of a dedicated local tolerance study for GBP510 can be endorsed. Local tolerance was evaluated as part of the repeat dose GLP toxicology studies in rats.

Nevertheless, in the RMP a stand-alone local tolerance study in rabbits was described. This study report should be provided.

3.2.5. Ecotoxicity/environmental risk assessment

In accordance with CHMP guidance EMEA/CHMP/SWP/4447100 entitled, "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" published 01 June 2006, due to their nature, vaccines are unlikely to result in a significant risk to the environment. Therefore, the absence of an environmental risk assessment is agreed with.

3.2.6. Discussion on non-clinical aspects

Several of the non-clinical studies (pharmacology as well as toxicity) were performed using non-clinical batches. No quality characterisation data was available for these batches. The Applicant should discuss whether the quality of these non-clinical batches is sufficiently representative of the clinical batches. See also quality MO and OC regarding the manufacture and pharmaceutical development of the drug product. In addition, the Applicant should i) describe the differences between the preclinical (AS03A) and the clinical (AS03) adjuvant batch by clarifying the meaning of the so-called "A" in the final formulation used in the non-clinical studies; and ii) discuss to what extent the peptide linker between the RBD and I53-50A may be degraded by enzymes. (OC)

The neutralising capacity of anti-RBD antibodies is evaluated with PBNA and PRNT assays, but there is no clear trend in results between these two assays and between the preliminary and confirmed results from the PBNA assay. This subverts the reliability of the corresponding data. The Applicant should i) justify why the Applicant did not select a single method of measurement of neutralising antibodies, and ii) clarify the differences between the WT strains used (ancestral, D614G, Wuhan, Korea/KCDC03/2020, etc.). (OC)

The two immunogenicity studies in female BALB/c mice demonstrated that a two-dose regimen elicited a higher humoral immune response compared to a single dose, supporting the value of a second injection. Additionally, the total antibody and neutralising antibody response was higher in AS03-adjuvanted formulations when compared to alum-adjuvanted formulations or non-adjuvanted formulations, supporting the use of AS03 in the clinic. In general, the humoral response between non-clinical and clinical formulations showed a similar trend. In the study with the non-clinical formulation (Study RSR510.04.03), a mixed Th1/Th2 response was induced. Data on the cell-mediated immune response was not obtained in the study with the clinical formulation. Considering the limited cell-mediated response data and the difference in antigen:adjuvant ratio in the non-clinical formulation compared to clinical batches, the relevance of the data from Study RSR510.04.03 for the clinic remains unclear and no clear conclusion can be made with respect to a potential risk for VAERD. However, when considering the clinical experience, interim results from the Phase I/II clinical trial suggest that alum and AS03-adjuvanted vaccine formulations induce the production of IL-2 and TNF-α which is suggestive of a Th1 response, whereas IL-5 response was low, and IL-4 response was inconsistent.

Overall, the immunogenicity results in female K18-hACE2 TG mice (Study RSR510.04.04) were similar to those in the immunogenicity studies in female BALB/c mice (Study RSR510.04.03); they

demonstrated that a two-dose regimen elicited a higher humoral immune response compared to a single dose, supporting the need for a second injection. Additionally, the total antibody and neutralising antibody response was higher in AS03-adjuvanted formulations when compared to alum-adjuvanted formulations, supporting the use of AS03 in the clinic. It should be noted however, that the immunogenicity results in cynomolgus monkey demonstrated a more pronounced response with the alum-adjuvanted clinical formulation.

The cell-mediated immune response was evaluated in the study with the clinical formulation in cynomolgus monkey. However, the data showed high variability and was considered too limited. Therefore, no clear conclusion can be made with respect to a potential risk for VAERD.

The challenge studies in female K18-hACE2 TG mice immunised with either alum- or AS03-adjuvanted clinical or non-clinical formulations demonstrated effective prevention against mortality, reduced body weight and temperature, increased lung viral load and histopathological alterations in the lung. Vaccination with alum- or AS03-adjuvanted clinical formulations also conferred immune protection against subsequent challenge with alpha and beta variants of SARS-CoV-2, whereby AS03-adjuvanted formulations showed slightly higher protection. It should be noted that only a single route (intranasal) of challenge was evaluated in mice.

In the challenge study in cynomolgus monkeys, the alum-adjuvanted clinical formulation appeared slightly more effective compared to AS03-adjuvanted GBP510, based on viral load in the nose and throat. However, this study has several limitations. No other parameters than viral load in upper airways were evaluated post-challenge in the monkeys. The study report states that clinical signs were monitored after the challenge, however these data are not described. Moreover, no viral load in the lower respiratory tract was determined, nor lung histopathology was performed. In addition, the Applicant used a challenge dose of $2.6x10^6$ $TCID_{50,}$ with reference to a study in rhesus monkeys (Van Doremalen et al., 2020), however it is not known whether this dose is also sufficient to induce clinical symptoms and lung pathology in cynomolgus monkeys. Taken together, no final conclusions can be drawn regarding the protective effect of the vaccine against COVID disease. Therefore, the Applicant is asked to justify the design of the challenge studies (including challenge dose, route of administration, location of sampling, monitored pre- and post-challenge parameters/clinical signs) in the light of natural SARS-CoV-2 infection and the pathology observed in humans, and subsequently discuss the clinical relevance of the studies in NHPs (OC).

In conclusion, studies conducted in the rodent and non-human primate showed that IM administration of two doses of AS03-adjuvanted RBD-NP or GBP510 stimulated the production of binding and neutralising antibodies. In addition, there was evidence of a cell-mediated response (mixed Th1/Th2 response). Vaccination with adjuvanted RBD-NP or GBP510 induced immune protection from SARS-CoV-2 challenge with the WT, alpha or beta variant and reduced mortality and viral load in the upper respiratory tract in mice. The design of the challenge study in cynomolgus monkeys is considered too limited, and therefore the value of this study is questioned.

Several studies were conducted in rodents and non-human primates to support the use of a third vaccine dose. It should be mentioned that the study designs do not reflect the booster setting in humans very adequately, since the third dose (referred to as booster dose by the Applicant) is given relatively early in the animals (more or less as part of the 'primary' vaccination regimen), which is not likely the case in humans (i.e. duration interval between second and third dose will be longer, thus a real booster). This could impact the (hight of the) immune response and thus the efficacy of the vaccine.

Since there is limited data obtained in the challenge studies, the Applicant is asked to further clarify the results obtained in the challenge study in K18-hACE2 TG mice, and provide a more elaborate discussion on the relevance of the study design and results for evaluation of vaccine efficacy (OC).

In conclusion, a third dose led to increased humoral immune response and viral clearance in both species, although the clinical relevance of the study design, including dose regimen (interval) used in these studies, is questioned. In a perspective of a future application for a booster dose, the Applicant would have to discuss to what extend the used 21-day schema between the two doses in mice followed by the 21-day booster and the two-dose 28-day schema plus the 28-day interval for the booster used in monkeys can be extrapolated and mimic that intended in humans.

In repeated dose toxicity study 20-RR-0828 a significant reduction in urine volume was noted in females only and this effect was attributed to an increase in body temperature. In contrast, in the study 20-RR-0935 a significant increase in urine volume was noted in females only with no change in water consumption or effects on the kidney. The increase in urine volume in the unadjuvanted females in study 20-RR-0935 is mainly caused by a larger urine volume in 1 animal. In addition, it is noted that in some of the control groups, the range in urine volume is very wide (up to a 6 times difference between lowest and highest value), indicating that normal values for urine volume can differ substantially. Since no histopathological changes to kidney or bladder were observed and no effects were observed in the adjuvanted groups, in males, or in any of the recovery groups, both the lower and higher urine volumes are however not considered to be toxicologically relevant.

In addition, testicular weight (absolute and relative) was decreased in the adjuvanted group in study 20-RR-0935 and relative testicular weight was reduced in the unadjuvanted recovery group. The decrease in (left) testicular weight in the adjuvanted group is caused by 1 animal. Left and right testes weight of all other animals is in the range of control animals. Furthermore, besides atrophy/degeneration in the single small left testis, no histopathological changes could be found. In the recovery group, testes weight (both absolute and relative) of the adjuvanted group was similar to the control group. Although relative testes weight of the unadjuvanted recovery group was slightly decreased, absolute testes weight was normal and no histopathological changes were observed. In addition, a similar effect was not observed in study 20-RR-0828. It is therefore unlikely that the effect is caused by the vaccine.

The dose level used in the reproductive and developmental toxicity study was 30 µg GBP510 (0.5 ml), except for the AS03-adjuvanted GBP510 group, which received only 12 µg (0.2 ml), which is lower than the intended clinical dose (25 µg). The fact that 30 µg in 0.5 ml is used for the other adjuvant groups as well as for the AS03-adjuvanted GBP510 group in the repeated dose toxicity studies shows that limitation due to volume is not an issue. It is noted that the WHO guidelines on non-clinical evaluation of vaccines indicate that 'the highest dose (in absolute terms) to be used in the proposed clinical trial should be evaluated in the animal model'. The Applicant should, therefore, justify this lower dose and its relevance for the clinic, considering the tendencies to increased incidences of foetal external abnormalities, foetal visceral variations and skeletal retardations reported in some GBP510-treated groups (including convoluted ureters observed in the AS03-adjuvanted GBP510 group). In addition, it is not clear why an Alum vehicle control group is included but not an AS03 vehicle control group, because AS03 is the adjuvant of choice in clinical studies. This should also be justified (OC).

The Applicant has described all safety-related studies and findings in Table 6 in RMP Part II: Module SII - Non-Clinical Part of the Safety Specification. However, this table is too extensive. According to the EMA Guideline on good pharmacovigilance practices (GVP), the RMP module SII "Non-clinical part of the safety specification", should only present a high-level summary of the significant non-clinical safety findings. Only relevant results, but no details on study design should be included. The Applicant is requested to update module SII (OC)

In the RMP, several studies have been mentioned that are relevant for the evaluation of safety of the current GBP510 vaccine adjuvanted with AS03; however, the studies could not be assessed since the reports were not provided. The Applicant is requested to submit the following study reports: the

scaffold 3-dose study and the double dose studies (studies 20-RR-1434, 21-RR-0342 and 21-RR-0502) and the local tolerance study in rabbits (Study 20-BL-1178). In addition, these data and their relevance for the clinic should be discussed in the RMP and in the NC overview/module 2.6. The studies with the variant vaccines are not needed for the current indication; therefore, there is no need to include them in the RMP and NC overview (OC).

3.2.7. Conclusion on non-clinical aspects

Assessment of the pre-clinical dossier revealed no major objections to marketing authorisation. However, several other concerns were identified. Once these issues are sufficiently addressed, there are no objections to marketing authorisation from a non-clinical point of view.

3.3. Clinical aspects

- **Tabular overview of clinical studies**

Table 1. Overview of submitted clinical trials

Study ID	No. of study centres / locations	Design	Study Objective	Study Posology (2 IM doses at 4-week interval)	Subjs by arm randomised	Gender M/F (n/n) Median Age	Primary Endpoint
GBP510_001	14 South Korea	Randomised observer-blinded placebo-controlled	Primary (safety): To assess the reactogenicity and safety profile of GBP510 vaccines in healthy younger adults post each vaccination. Secondary (immunogenicity): To assess the immunogenicity of GBP510 vaccines in healthy younger adults post each vaccination	10 µg GBP510 + Alum	102	51/51 40.5 yrs	AEs (solicited, unsolicited) AESIs, MAAEs, SAEs, deaths, MAADRs, vital signs, ECG, physical examination, and clinical safety laboratory parameters
				25 µg GBP510 + Alum	99	40/59 47.0 yrs	
				Placebo	59	36/23 41.0 yrs	
GBP510_002	14 South Korea	Randomised double-blind placebo-controlled	Primary (safety): To assess the reactogenicity and safety profile of GBP510 vaccines in healthy younger adults post each vaccination Secondary (immunogenicity): To assess the immunogenicity of GBP510 vaccines in healthy younger adults post each vaccination	10 µg GBP510 + AS03	101	51/50 44.0 yrs	AEs (solicited, unsolicited) AESIs, MAAEs, SAEs, deaths, MAADRs, vital signs, ECG, physical examination, and clinical safety laboratory parameters
				10 µg GBP510 (no AS03)	10	3/7 40.5 yrs	
				25 µg GBP510 + AS03	104	45/59 42.0 yrs	
				25 µg GBP510 (no AS03)	52	23/29 42.0 yrs	
				Placebo	61	26/35 42.0 yrs	
				Booster 25µg GBP510 + AS03	81	37/44 42.0 yrs	
GBP510_003	16 South Korea 3 Philippines 1 Vietnam 7 Ukraine 7 New Zealand 4 Thailand	Randomised double-blind active-controlled	Primary (immunogenicity): To demonstrate that the immune response induced by 2 doses of GBP510 25 µg adjuvanted with AS03 at 4-week interval in seronegative adults aged 18 years and older is superior (GMT) and non-inferior (SCR) to the immune response induced by 2 doses of ChAdOx1-S Secondary (safety): To assess the safety profile of GBP510 in adults aged 18 years and older regardless of serostatus at baseline	25 µg GBP510 with AS03	3,039	1814/1225, 36.0 yrs	• For superiority: GMT of neutralising antibody to the SARS-CoV-2 measured by wildtype virus assay 2 weeks post 2nd vaccination. • For non-inferiority: SCR (percentage of subjects with ≥ 4-fold rise from baseline) in wild-type virus neutralising antibody titre from baseline to 2 weeks post 2nd vaccination.
				CHAdOx1-S 5 × 10^{10} vp	997	572/425, 38.0 yrs	

3.3.1. Clinical pharmacology

3.3.1.1. Pharmacokinetics

No pharmacokinetics studies have been conducted for GBP510. This is because pharmacokinetics studies are generally not needed for vaccines, consistently with current Guidelines on clinical evaluation of vaccines

3.3.1.2. Pharmacodynamics

The pharmacodynamic profile of vaccines is defined by their immunogenicity, as detailed in the CHMP guideline "Guideline on Clinical Evaluation of New Vaccines" (EMEA/CHMP/VWP/164653/2005).

Mechanism of action

GBP510 contains a self-assembling, two-component nanoparticle (RBD-16GS-I53-50) presenting RBD. RBD-16GS-I53-50 is comprised of trimeric Component A (RBD-I53-50A) and pentameric Component B (I53-50B), self-assembled to display 60 copies of the SARS-CoV-2 S protein RBD. Component A, expressed in CHO cells, displays genetically fused RBD protein, and Component B, expressed in E. coli, forms a nanoparticle structure.

The vaccine is adjuvanted with AS03 in order to boost the immune response. AS03 is a squalene-based adjuvant, manufactured by GlaxoSmithKline (GSK), and enhances the immune response by increasing RBD-specific IgG and T-cell response through an antigen-sparing effect (Cohet et al., 2019). AS03 Adjuvant System contains a surfactant, polysorbate 80 and two biodegradable oils, α-tocopherol and squalene in a phosphate-buffered saline as the aqueous carrier. AS03 adjuvant capabilities derive from the oil-in-water phase as well as from α-tocopherol.

This adjuvant has been used in GSK's Pandemrix, pandemic A/H1N1 influenza vaccine and Prepandrix, pre-pandemic A/H5N1 influenza vaccine. There is extensive safety data available from the clinical development programme of AS03-adjuvanted vaccines against different influenza subtypes and from post-licensure experience, including pharmacovigilance and safety studies of AS03-adjuvanted A/H1N1pdm09 vaccines (Cohet et al., 2019).

Neutralising antibody response to the parental D614G strain, as well as cellular immune responses (Th1) are elicited following administration of this vaccine, which may contribute to protection against COVID-19.

To date, there is no established correlate of protection for COVID-19.

Assays

Several bioanalytical methods were used to support the clinical development of GBP510. Evaluation of neutralising antibody responses forms the basis of immunobridging of GBP510 to ChAdOx1-S in the Phase 3 study to support licensure. Cell mediated immune responses are investigated to provide further support. Below, a description and assessment of the main immunological assays that have been used to characterise the immunogenicity of GBP510 (and ChAdOx1-S) are provided.

For the phase III study SARS-CoV-2-neutralising antibodies were assessed by focus-reduction neutralisation test (FRNT). This assay is of pivotal importance as it is the basis for inference of efficacy. Further, fluorescence activated cell sorting (FACS) was used for evaluation of CMI and FluoroSpot was added for data reinforcement. An ELISA was used in all clinical studies for the determination of specific

IgG antibodies against S protein or N protein in human serum. The table below (Table 2) provides an overview of the assays and their validation status.

Table 2. Overview of bioanalytical methods used in the clinical development programme

Assay		Used in	Validation status
Humoral	FRNT	Phase III	Validated
	ELISA	Phase I/II/III	Validated
	PBNA	Phase I/II	Qualified
	PRNT	Phase I/II	Qualified
Cell mediated	ICS (FACS)	Phase I/II/III	Validated
	FluoroSpot	Phase III	Validated

The **focus-reduction neutralisation test (FRNT)** was performed at the Korean National Institute of Health and the International Vaccine Institute. FRNT is the pivotal assay used as part of the phase III study for the assessment of neutralising antibodies in serum induced after vaccination by using wild-type viruses. The assay measures the ability of serum to inhibit infection of Vero cells with wildtype SARS-CoV-2. The test method was validated by verifying the following parameters: dilutional linearity, relative accuracy, repeatability, precision, specificity, matrix interference, sample stability and robustness.

The SARS-CoV-2 IgG **Enzyme Linked ImmunoSorbent Assay (ELISA)** was performed at the sponsor laboratory. The assay measures the amount of Spike-binding antibody in serum. The test method was validated by verifying the following parameters of the standardised IgG ELISA test method that has been qualified earlier: specificity, accuracy, dilutional linearity/relative accuracy, precision/repeatability, LLOQ/ULOQ verification, sample stability, robustness.

The **Pseudovirus-based neutralisation assay (PBNA)** was performed at the sponsor laboratory. PBNA is an assay to measure the neutralising antibody titres by using a genetically modified virus that is incapable of self-replicating. In the Applicant's assay, a Vesicular Stomatitis Virus (VSV) backbone was used for the PsV. The assay measures the ability of serum to inhibit infection of HEK 293/ ACE2 cells with the SARS-Co V-2 Pseudovirus. Only a qualification report was available.

The **Wild-type virus Plaque Reduction Neutralisation Test (PRNT)** was performed at the Zoonosis Research Institute, Jeonbuk National University. The assay measures the ability of serum to inhibit infection of Vero cells with wildtype SARS-CoV-2 by measuring the plaque form of Cytopathic Effect (CPE) that appears when the virus infects cells. Only a qualification report was available.

The **Intracellular Cytokine Staining (ICS) assay** was performed at the sponsor laboratory (SK Bioscience). The ICS assay measures the percentage of cytokine positive T cells in Peripheral Blood Mononuclear Cells (PBMC) samples by fluorescence activated cell sorting (FACS). The ICS assay validation was based on examination of the following parameters: Linearity, Specificity, Inter-analyst precision, Inter-day precision, Repeatability.

The **FluoroSpot assay** was performed at the sponsor laboratory (SK Bioscience). The FluoroSpot Assay is a modified method of an ELISpot Assay. The assay detects cytokines (IFN-y, IL-2, TNF-a and IL-4) that are secreted from single T cells. One or more cytokines can be detected simultaneously since several antibodies are conjugated with different type of fluorophores, which allows to detect T cells producing various cytokines. Secretory activity of a single cell can be measured by fluorescent spots on

a plate membrane. For the validation of the FluoroSpot assay the following parameters were examined: Precision, Repeatability, Dilutional Linearity, Relative Accuracy and Specificity.

3.3.2. Discussion on clinical pharmacology

In the context of vaccines, PK studies are not required because the PK is not considered informative towards the determination of an optimal dose and the metabolic pathways of vaccines are generally understood.

As this application is based on immunobridging, in which the immune response elicited by GBP510 is compared to the immune response elicited by ChAdOx1-S in order to infer efficacy, the immunological assays are of pivotal importance.

The Applicant provided data from an ELISA, FRNT assay and ICS/FACS supported by FluoroSpot for their pivotal phase III study. Although the Applicant claims that the assays were validated and are considered valid for the intended use to support the immunobridging approach, several issues have been raised. In general, for none of the validated assays it is clear on what basis the acceptance criteria were set. This should be properly justified for each of the validated assays. **(MO for FRNT assay, OCs for the other assays)**

Regarding the FRNT assay – the assay providing the pivotal immunogenicity data – a few additional issues need to be resolved. The Applicant is requested to provide the LLOQ and ULOQ as well as the LOD of the FRNT assay. Also, the strain of the in house SARS-CoV2 virus as well as the neutralising activity of the in house QC serum are unknown and more details should be provided. Further, during the presubmission meeting the Applicant committed to include in the dossier a demonstration of surrogacy of the FRNT assay for a conventional wild-type virus neutralisation assay. This could however not be located in the dossier. These issues are raised as **MO** given the importance of the assay for the inference of efficacy. The primary endpoint in the phase 3 study is depicted as international units (IU)/mL. This is generated by multiplying the raw FRNT50 values for each of the samples with a Conversion Factor calculated using a 'KDCA National Standard' that is included in each of the plates.

In scientific advice it was stated that 'given the lack of an ICP, full characterisation of the immune response is highly relevant', and the proposed cell mediated immunity (CMI) analyses were endorsed. To characterise CMI, the Applicant used an intracellular cytokine staining (ICS) assay as well as a FluoroSpot assay, both which are fully validated according to the Applicant. For both assays the validation report was submitted and assessed.

3.3.3. Conclusions on clinical pharmacology

The pivotal evidence in support of this MAA comes from the FRNT assay, in which the ability of serum to inhibit infection of Vero cells with wildtype SARS-CoV-2 was assessed. Samples derived from subjects vaccinated with GBP-510 were compared with samples derived from subjects vaccinated with Vaxzevria, for which efficacy has been established. Based on the principle of immunobridging, if GBP-510 vaccinated samples would show a similar or higher neutralising capacity compared to Vaxzevria vaccinated samples, at least a similar level of efficacy can be inferred. Further, as full characterisation of the immune response is considered highly relevant, cell-mediated immunity was also investigated.

Several questions have been raised regarding the bioanalytical methods that have been used. These need to be resolved before the assays can be considered adequate to describe the vaccine-induced immune response.

3.3.4. Clinical efficacy

3.3.4.1. Dose-response studies

Study GBP510_002 is a first-in-human, Phase I/II multicentre (14 sites, South Korea), randomised, placebo-controlled, observer-blinded study designed to assess the safety, reactogenicity and immunogenicity of a GBP510 adjuvanted with or without AS03 in healthy younger and older adults. The trial consisted of three stages with a stepwise precautionary approach for safety.

A total of 320 healthy adults were planned to be enrolled and randomised in stage 1 and stage 2.

Randomisation was in a 2:1:1 ratio for Stage 1 to two IM injections at a 4-week interval of either 10 µg GBP510 with or without AS03, 25 µg GBP510 with or without AS03, or placebo (normal saline). In Stage 2, randomisation was at a 2:2:1:1 ratio, to 10 µg GBP510 with AS03, 25 µg GBP510 with or without AS03, or placebo (normal saline). The 10 µg GBP510 group without AS03 was included only in Stage 1.

Stage 3 has been designed to evaluate a booster dose and includes approximately 100 subjects aged 19 to 85 years who had received a primary series of 25 µg GBP510 with AS03. These data are not yet available.

Serum was collected at multiple timepoints: Visit 2(pre-1st dose), Visit 4 (pre-2nd dose), Visit 6 (2-week Follow up), Visit 7 (4-week Follow-up), Visit 8 (3-month Follow-up), Visit 9 (6-month Follow-up), and Visit 10 (12-month Follow-up). The immune response was characterised with an ELISA and an unvalidated pseudovirus (PNBA) assay measuring neutralising antibodies. The results up to visit 7 (4 weeks post-dose 2) are available.

Results

A total of 328 people were enrolled and randomly assigned for stage 1 and 2, and all were included in the ITT dataset, the PP set consisted of 302 participants. Overall, demographic and baseline characteristics were comparable between treatment groups. The mean age (SD) of the study population was 43.9 (14.5) years and the majority of included subjects were between 19 and 64 years of age. All subjects were Korean.

Considering the RBD IgG antibody titer as measured by ELISA, higher GMTs and GMFRs were observed in GBP510 25 ug with AS03 group when compared to the non-adjuvanted and GBP510 10 ug with AS03 groups at two and four weeks after Dose 2 (visit 6 and 7, respectively; Table 3). The SCRs were >99% in both adjuvanted groups.

Among all treatment arms, GMT of neutralising antibody titer by PBNA at Visit 6 (2 weeks post-2nd vaccination) showed the highest value, with similar GMTs in the 10µg+AS03 and 25µg+AS03 group. At visit 7 (4 weeks post 2nd dose), titres had declined and remained numerically highest in the 25µg+AS03 arm (GMT=1,107 compared with 839 in the 10µg+AS03 arm and 62/59 in the unadjuvanted arms).

Table 3. Geometric Mean Titre and Seroconversion rate of IgG antibody titre to the SARSCoV-2-RBD by ELISA (PP Set)

		GBP510 10ug with AS03 (N=96)	GBP510 10ug (N=10)	GBP510 25ug with AS03 (N=96)	GBP510 25ug (N=45)	Placebo (N=58)
Baseline	N	93	10	96	45	58
	GMT	15.1	11.0	13.9	16.3	12.5

	95% CI	(13.5, 16.8)	(7.8, 15.4)	(12.4, 15.5)	(14.0, 19.0)	(11.0, 14.3)
Visit 6 (2 weeks post dose 2)	N	93	10	96	45	58
	GMT	2,163.6	155.3	2,599.2	112.4	10.6
	95% CI	(1,898.1, 2,466.2)	(70.0, 344.5)	(2,292.6, 2,946.8)	(82.9, 152.4)	(9.3, 12.0)
	GMFR	143.5	14.2	187.6	6.9	0.8
	95% CI	(120.5, 170.9)	(7.2, 27.9)	(161.6, 217.8)	(5.0, 9.5)	(0.7, 1.0)
	SCR, n(%)	93 (100.0)	10 (100.0)	96 (100.0)	29 (64.4)	0 (0.0)
	95%CI	(96.1, 100.0)	(69.2, 100.0)	(96.2, 100.0)	(48.8, 78.1)	(0.0, 6.2)
Visit 7 (4 weeks post dose 2)	N	93	10	96	45	58
	GMT	1,517.9	132.6	1,943.4	115.0	12.5
	95% CI	(1,304.7, 1,765.9)	(64.2, 273.9)	(1,727.7, 2,186.1)	(84.9, 155.7)	(10.9, 14.4)
	GMFR	100.7	12.1	140.3	7.0	1.0
	95% CI	(83.0, 122.0)	(6.5, 22.5)	(121.1, 162.4)	(5.1, 9.7)	(0.8, 1.2)
	SCR, n	92 (98.9)	10 (100.0)	96 (100.0)	28 (62.2)	1 (1.7)
	95%CI	(94.2, 100.0)	(69.2, 100.0)	(96.2, 100.0)	(46.5, 76.2)	(0.0, 9.2)

GMT = geometric mean titre; GMFR = GMFR (Geometric Mean Fold Rise) = GMT (visit) / GMT (Baseline)

Table 4. Geometric Mean Titre and Seroconversion rate of neutralising antibody titre to the SARS-CoV-2 by PBNA (PP Set)

		GBP510 10ug with AS03 (N=96)	GBP510 10ug (N=10)	GBP510 25ug with AS03 (N=96)	GBP510 25ug (N=45)	Placebo (N=58)
Baseline	N	93	10	96	45	58
	GMT	18.1	21.0	19.5	19.1	19.2
	95% CI	(17.2, 19.0)	(15.2, 29.1)	(18.1, 21.0)	(16.9, 21.4)	(17.2, 21.4)
Visit 6 (2 weeks post dose 2)	N	93	10	96	45	58
	GMT	1,369.0	83.5	1,431.5	63.9	19.2
	95% CI	(1,124.5, 1,666.7)	(28.6, 243.5)	(1,171.1, 1,749.7)	(44.6, 91.5)	(17.4, 21.3)
	GMFR	75.8	4.0	73.4	3.4	1.0
	95% CI	(61.9, 92.9)	(1.5, 10.9)	(59.3, 91.0)	(2.3, 4.9)	(0.9, 1.1)
	SCR, n (%)	93 (100.0)	5 (50.0)	95 (99.0)	23 (51.1)	1 (1.7)
	95%CI	(96.1, 100.0)	(18.7, 81.3)	(94.3, 100.0)	(35.8, 66.3)	(0.0, 9.2)
Visit 7 (4 weeks post dose 2)	N	93	10	96	45	58
	GMT	838.8	68.5	1,107.3	51.9	19.3
	95% CI	(681.7, 1,032.1)	(26.1, 179.8)	(911.4, 1,345.3)	(36.1, 74.6)	(17.4, 21.4)
	GMFR	46.5	3.3	56.8	2.7	1.0
	95% CI	(37.6, 57.4)	(1.2, 9.0)	(45.6, 70.7)	(1.8, 4.0)	(0.9, 1.2)

	SCR, n	91 (97.9)	5 (50.0)	95 (99.0)	19 (42.22)	2 (3.45)
	95%CI	(92.5, 99.7)	(18.7, 81.3)	(94.3,100.0)	(27.7, 57.9)	(0.4, 11.9)

GMT = geometric mean titre; GMFR = GMFR (Geometric Mean Fold Rise) = GMT (visit) / GMT (Baseline)
a. The 95% CI for GMT/GMFR is calculated based on the t-distribution of the log-transformed values, then back transformed to the original scale for presentation.
b. The 95% CI for SCR is calculated by Clopper-Pearson Methods

Submitted CMI data (only shown in Clinical AR for phase 2) suggested that in CD4+ cells, both adjuvanted doses of vaccine induced cytokine production with a dominant Th1 profile.

The GBP510 25 µg adjuvanted with AS03 group was chosen for evaluation in the pivotal Phase III study.

3.3.4.2. Main study

GBP510_003

Methods

GBP510_003 is a randomised active-controlled, observer-blind, multi-centre study to assess the immunogenicity and safety of SK SARS-CoV-2 recombinant protein nanoparticle vaccine adjuvanted with AS03 (GBP510) in adults aged 18 years and older. The study involved two cohorts. Cohort 1 (immunogenicity cohort) includes only participants with no history of SARS-CoV-2 infection and COVID-19 vaccination confirmed by a SARS-CoV-2 rapid antibody kit at screening, for cohort 2 (safety cohort) participants were enrolled regardless of their serostatus.

Study Participants

A total of 38 centres screened and enrolled participants in six countries (South Korea, Philippines, Vietnam, Thailand, Ukraine, New Zealand).

Participants aged 18 years or older were eligible for inclusion if they were healthy or medically stable, not pregnant or breastfeeding and using adequate contraception (female participants only).

Participants for Cohort 1 were not to have a history of SARS-CoV-2 infection or vaccination, confirmed by a positive result of qualitative test for SARS-CoV-2 antibody using a rapid antibody kit at screening.

Participants were not to have 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 history of SARS or MERS disease or vaccination, or a history of relevant medical conditions: congenital, hereditary, acquired immunodeficiency, or autoimmune disease; bleeding disorder including thrombocytopenia which is contraindicating intramuscular vaccination; thrombosis, immune thrombocytopenia, or capillary leak syndrome which is contraindicating ChAdOx1-S vaccination; hypersensitivity and severe allergic reaction to any vaccines or components of the study vaccine; malignancy within 1 year prior to the 1st study vaccination with a risk of recurrence.

Participants were excluded upon receipt of any medications or vaccinations intended to prevent COVID-19, any vaccine within 4 weeks prior to the 1st study vaccination or planned receipt of any vaccine from enrolment 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.

Participants were excluded upon receipt of immunoglobulins and/or any blood or blood products within 12 weeks prior to the 1st study vaccination or chronic use (more than 2 consecutive weeks) of immunosuppressive therapy, such as anticancer 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 was permitted.

Treatments

Participants in the immunogenicity cohort were randomised (2:1 ratio) to 2-doses of GBP510 (vaccine candidate, 25µg + AS03) or ChAdOx1-S (control vaccine, 5×10^{10} viral particles per dose corresponding to not less than 2.5×10^{8} infectious units) administered by intramuscular injection 28 days apart. The injection volume was approximately 0.5 mL.

The following lot numbers were used for this study: CTIAV5002; CTIAV5005; CTIAV5006 (GBP510), AA03G053B (AS03), CTMAV577; CTMAV588; CTMAV5108 (ChAdOx1-S).

Objectives

Only immunogenicity objectives are listed here.

Primary objectives:

To demonstrate that the immune response induced by 2 doses of GBP510 25µg adjuvanted to AS03 at 4-week interval in seronegative adults aged 18 years and older is both superior with regard to GMT ratio's and non-inferior to the immune response (seroconversion rate) induced by 2 doses of ChAdOx1-S, using two co-primary objectives:

- Superiority of GBP510 in GMT is proven if the lower limit of 2-sided 95% Confidence Interval (CI) of the adjusted GMT ratio (GBP510/ChAdOx1-S) is greater than 1 on Visit 6 (2 weeks after 2nd vaccination).
- Non-Inferiority of GBP510 in the proportion of the participant with $\geqslant$ 4-fold rise (seroconversion rate, %) is proven if the lower limit of 2 sided 95% CI for the difference in two groups (GBP510 - ChAdOx-1) is greater than -5.0% on Visit 6 (2 weeks after 2nd vaccination).

Secondary objectives:

- To assess and compare the immune responses induced by 1 or 2 doses of GBP510 with ChAdOx1-S in seronegative adults aged 18 years and older
- To assess and compare the immune responses induced by 1 or 2 doses of GBP510 with ChAdOx1-S in seronegative adults aged 18 through 64 years
- To assess and compare the immune responses induced by 1 or 2 doses GBP510 with ChAdOx1-S in seronegative adults aged 65 years and older

Exploratory objectives:

- To describe the immune responses induced in adults aged 18 years and older who proved to be seropositive prior to study vaccination and/or to be infected during the study
- To describe the immune responses against the circulating strains, including the variants of concern
- To compare the incidence rates of virologically-confirmed COVID-19 between GBP510 and ChAdOx1-S
- To describe the consistency of immunogenicity across ethnicities

Outcomes/endpoints

Primary endpoints:

For all participants of Cohort 1, there are 2 co-primary endpoints

- GMT of neutralising antibody to the SARS-CoV-2 measured by wild-type virus neutralisation assays 2 weeks post 2nd vaccination
- Percentage of participants with ⩾ 4-fold rise in wild-type virus neutralising antibody titre from baseline to 2 weeks post 2nd vaccination

Secondary endpoints:

Only in all participants of Cohort 1 at the following time points after study vaccination: 4 weeks post 1st vaccination; 2 weeks, 4 weeks, 6 months, and 12 months post 2nd vaccination;

- GMT of SARS-CoV-2 RBD-binding IgG antibody measured by ELISA at each time point post-vaccination
- GMFR of SARS-CoV-2 RBD-binding IgG antibody measured by ELISA from baseline to each subsequent time point postvaccination
- Percentage of participants with ⩾ 4-fold rise in ELISA SARS-CoV-2 RBD-binding IgG titre from baseline to each subsequent time point post-vaccination
- GMT of neutralising antibody to the SARS-CoV-2 measured by wild-type virus neutralisation assays at each time point postvaccination
- GMFR of neutralising antibody to the SARS-CoV-2 measured by wild-type virus neutralisation assays from baseline to each subsequent time point post-vaccination
- Percentage of participants with ⩾ 4-fold rise in wild-type virus neutralising antibody titre from baseline to each subsequent time point post-vaccination

Only in a subset of 10% participants of Cohort 1 at the following partial time points after study vaccination: 2 weeks, 6 months, and 12 months post 2nd vaccination

- Cell-mediated response for both Th1 and Th2 cytokines (including but not limited to INF-γ, TNF-α, IL-2, and IL-4 produced by T lymphocytes) measured by ELISpot and/or FluoroSpot, and for both CD4+ and CD8+ T-cells measured by FACS.

Exploratory endpoints:

COVID-19 incidence rate: The incidence rates and severities were to be estimated based on any symptomatic SARS-CoV- 2 infection diagnosed ⩾ 14 days after completion of the 1st or 2nd study vaccination. The severity of COVID-19 cases will be categorised using the WHO severity definitions based on clinical indicators.

If a participant experiences a suspicious symptom of COVID-19, or is notified as having a potential contact with COVID-19 patients, the participant should take examination according to applicable local law and regulations. The participant will be instructed to contact the investigator immediately to notify the fact that the symptoms occurred. Signs and symptoms of COVID-19 may vary. If the virological (PCR) test result is confirmed as positive, the case will be considered and collected as a confirmed-COVID-19.

Sample size

This study is powered to achieve overall 90% power (almost 95% power for each endpoint) to demonstrate both superiority and non-inferiority of the co-primary endpoints.

Sample size and power for Cohort 1 were estimated based on the results of neutralisation assays from the Phase 3 study of ChAdOx1-S and Phase 1 study GBP510_002; for the coprimary objectives of superiority (GMT) and non-inferiority (SCR) was estimated that a sample size of 9 (6 vs 3) and 231 was required for 95% power to detect superiority and non-inferiority respectively. It was determined to recruit approximately 1,950 participants (1,300 in Test group, 650 in Control group) to achieve a more conservative sample size.

Randomisation and blinding (masking)

Randomisation was stratified by age (18-64 or ⩾65 years) and trial site to pursue an approximately equal distribution of participants among the treatment groups within each age group and trial site.

The trial sites were priorly allocated to either Cohort 1 or 2, considering the respective number of participants planned for recruitment. For cohort 1, participants were centrally assigned to randomised (2:1) study intervention using an Interactive Response Technology, using pre-generated blocked randomisation schedules.

This study is observer-blinded. Only the study staff who received, stored, prepared, dispensed or administered the study intervention and who were not involved with the safety evaluation knew which study intervention was administered. It is to be noted that administrators were also unblinded. The protocol states that the study intervention should be administered in a manner that prevents the participants from identifying the type of study intervention by its appearance.

Statistical methods

Analysis sets

For analysis purposes several populations were defined (Table 5).

Table 5. Analysis populations

Population	Description	Analysis
ITT set	All participants who were randomised	
Safety Set	All participants who received at least 1 dose of study intervention	As treated
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	As randomised
Per-protocol set (PPS)	Two PPS were used: PPS1 for Primary stage (Visit 1 to 6) PPS2 for Extension stage (Visit 7 to 9) All participants who completed the vaccination schedule in an uninfected state with SARS-CoV-2 and had no major protocol deviations*	

*A participant was confirmed to be uninfected if the baseline neutralising antibody titre was below LLOQ in wildtype virus neutralisation assay, and no history of SARS-CoV-2 infection was confirmed by medical interview within the predefined period for PPS1 or PPS2 - A negative result in the immunoassay for the in vitro qualitative detection of antibodies to SARS-CoV-2 at Visit 6 was additionally required for PPS1.

Adjustment for multiplicity

No adjustment was made for multiplicity:

- No adjustment for multiple comparisons is required since both endpoints need to be significant to achieve study success
- For secondary endpoints no adjustment for multiplicity was performed.
- No adjustment for multiplicity on interim analysis has been performed for the primary endpoint

Analysis of the co-primary endpoints

This study aims to demonstrate both superiority and non-inferiority of the co-primary endpoints GMT of neutralising antibody to SARS-CoV-2 2 weeks post 2nd vaccination and percentage of participants with ⩾ 4-fold rise in neutralising antibody titre from baseline to 2 weeks post 2nd vaccination. Analyses were performed on the PPS1, with supplementary analysis on the FAS.

Co-primary endpoint 1: GMT
Hypothesis testing will be performed to assess superiority based on the 2-sided 95% CI of the ratio of post-vaccination GMT 2 weeks post 2nd vaccination (GBP510 over ChAdOx1-S) using 2-sided CIs at 0.05 significance level.

Adjusted estimates of GMTs, and their associated 95% CIs were determined using analysis of covariance (ANCOVA) model with treatment group, age group (18~64, ⩾65) as factors, and baseline antibody level as covariate. The ANCOVA model was fitted to the log-transformed value, then back to the original scale for presentation.

Additionally, adjusted GMTs, and their 95% CIs using ANCOVA with treatment group, age group, sex, race, and baseline antibody level will be presented.

Co-primary endpoint 2: Seroconversion
Hypothesis testing will be performed to assess non-inferiority based on the 2-sided 95% CI of the difference in the percentages of participants with ⩾ 4-fold rise from baseline to 2 weeks post 2nd vaccination (GBP510 – ChAdOx1-S) in neutralisation antibody titer, using 2-sided CIs at 0.05 significance level.

Percentage of participants with ⩾ 4-fold rise was calculated by dividing the number of participants with [(titer at Visit 6/titer at Visit 2) ⩾ 4] by the number of participants in analysis set with non-missing value at Visit 6 and Visit 2, multiplied by 100. The 95% CI of percentage of participants ⩾ 4-fold rises will be calculated based on Clopper-Pearson method. The 95% CI of difference in percentage of participants ⩾ 4-fold rises between groups will be calculated based on Chan and Zhang method.

Non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI for the difference of the percentage of participants with ⩾ 4-fold rise exceeded a non-inferiority margin of -5%.

Missing data is not imputed.

Analysis of secondary endpoints

For the secondary endpoints, the point estimates and their 95% CI of the parameters displayed in were presented for each treatment group. Analyses were performed on the PPS1, with supplementary analysis on the FAS.

The 95% CI was 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 were calculated based on Clopper-Pearson method.

Subgroup analyses

Planned subgroups are age group (18-64 years, ⩾ 65years), sex (male, female), and race (Asian, Caucasian). Subgroup analyses will be conducted for the primary and secondary immunogenicity endpoints (except CMI and FRNT50) on both PPS1 and FAS using the same analysis methods.

This study is will be conducted in three ethnicities, Southeast Asian, Caucasian, and Korean. A minimum proportion of Korean was included, to assess consistency of treatment effect across all ethnicities.

Results

Participant flow

Table 6. Study disposition (Cohort 1 and 2 combined)

	GBP510	ChAdOx1-S	Total
Screening			4913
Screening Failure			877
Primary Reason for Screening Failure[1)], n(%)			
Subject did not fulfil all eligibility criteria			401(8.16)
Withdraw consent			17(0.35)
Subject's conditions or other reasons for which conduct of required examination is not feasible			2(0.04)
Under PI decision			0
Others			457(9.30)
Randomised Set[2), 3)], n(%)	3039	997	4036
1st vaccination	3030(99.70)	995(99.80)	4025(99.73)
2nd vaccination	2900(95.43)	958(96.09)	3858(95.59)
Not vaccinated	9(0.30)	2(0.20)	11(0.27)
Status[2), 3)], n(%)			
Completion	2949(97.04)	969(97.19)	3918(97.08)
Discontinuation	90(2.96)	28(2.81)	118(2.92)
Primary Reason for Discontinuation[2), 3)], n(%)			
At the discretion of the investigator or sponsor due to safety concerns (i.e. AE/SAEs)	4(0.13)	2(0.20)	6(0.15)
Lost to follow-up	25(0.82)	5(0.50)	30(0.74)
At the discretion of the investigator or sponsor due to significant non-compliance with the protocol (i.e. refused / major protocol deviation including newly developed or not pre-identified exclusion criteria are met)	9(0.30)	3(0.30)	12(0.30)
At request of the participant	52(1.71)	16(1.60)	68(1.68)
Death	0	1(0.10)	1(0.02)
Pregnancy	0	0	0
Study termination by sponsor	0	0	0
Others	0	1(0.10)	1(0.02)

PI = principal investigator, AEs = adverse events, SAEs = serious adverse events.
Note: 1) Denominator of percentage is the number of screened participants.
2) Denominator of percentage is the number of randomised participants.
3) The number of participants were displayed according to planned treatment group. One participant was administered incorrect IP inconsistent (ChAdOx1-S) with randomisation assignment (GBP510).

Recruitment

Date of first participant enrolment: 30 August 2021

Date of Last Participant Last Visit (of interim analysis; Visit 7): 18 March 2022

The analyses presented in this report are based on a database lock date of 9 Apr 2022 for the immunogenicity cohort and 20 Apr 2022 for the safety cohort. The SAP was finalised on 11 April 2022.

The current interim CSR covers data until Visit 7 (4 weeks after 2nd vaccination) for safety set and Visit 6 (2 weeks after 2nd vaccination) for immunogenicity cohort (Cohort 1).

Conduct of the study

Compared to the first version of the protocol (dd 22-06-2021), important changes in version 1.1 (dd 21-07-2021) covered the change in post-vaccination timepoint (from 4 to 2 weeks post-vaccination) for the assessment of the co-primary endpoints. In addition, the sample size was updated based on the results of the phase I immunogenicity study.

For version 1.2 (dated 3-9-2021) the rapid antibody kit test was replaced by the in vitro qualitative immunoassay for SARS-CoV-2. In version 1.3 (dated 21-02-2022) follow-up and end of study visits for participants who requested to discontinue from the study for receiving a booster dose of other available COVID-19 vaccine have been defined.

Among the 4036 subjects enrolled and included in the ITT dataset, at least one major protocol deviation (a total of 968 events) occurred in 550 subjects (13.63%). Most common reported protocol deviation was "visit window deviation", followed by "Efficacy variables check" (Table 7).

Table 7. Participants with Major Protocol Deviations (ITT)

	GBP510 (N=3039)	**ChAdOx1-S (N=997)**	**Total (N=4036)**
Participants with Major Protocol Deviation	408(13.43) [719]	142(14.24) [249]	550(13.63) [968]
Visit Window Deviation	231(7.60) [243]	70(7.02) [72]	301(7.46) [315]
Efficacy Variables Check	115(3.78) [179]	44(4.41) [71]	159(3.94) [250]
Safety Variables Check	94(3.09) [128]	40(4.01) [46]	134(3.32) [174]
IP Administration Deviation	91(2.99) [103]	26(2.61) [34]	117(2.90) [137]
Other	39(1.28) [45]	14(1.40) [17]	53(1.31) [62]
Eligibility	9(0.30) [9]	3(0.30) [3]	12(0.30) [12]
Prohibited Medications	8(0.26) [8]	1(0.10) [1]	9(0.22) [9]
Exclusion Criteria Deviation	4(0.13) [4]	1(0.10) [1]	5(0.12) [5]
Test Window Deviation	0	1(0.10) [3]	1(0.02) [3]
Inclusion Criteria Deviation	0	1(0.10) [1]	1(0.02) [1]

Note: Protocol deviations are displayed as 'number of subjects(percentage of subjects) [number of event]

Baseline data

Table 8. Demographics and Baseline Characteristics (Cohort 1 and 2 combined) (Intention-to-Treat Set, GBP510_003)

	GBP510 (N=3039)	ChAdOx1-S (N=997)	Total (N=4036)
Age at randomisation (years)			
N	3039	997	4036
Mean (SD)	37.8 (13.8)	39.3 (13.8)	38.2 (13.8)
Median	36.00	38.00	37.00
Min, Max	18.00, 88.00	18.00, 87.00	18.00, 88.00
Age group at randomisation, n(%)			
18~64 years	2878(94.70)	943(94.58)	3821(94.67)
≥ 65 years	161(5.30)	54(5.42)	215(5.33)
Sex, n(%)			
Male	1814(59.69)	572(57.37)	2386(59.12)
Female	1225(40.31)	425(42.63)	1650(40.88)
Race, n(%)			
Asian	2856(93.98)	931(93.38)	3787(93.83)
Korean	329(10.83)	168(16.85)	497(12.31)
Southeast Asian	2526(83.12)	762(76.43)	3288(81.47)
Others	1(0.03)	1(0.10)	2(0.05)
Caucasian	177(5.82)	64(6.42)	241(5.97)
Black	0	0	0
Hispanic	0	0	0
Other	6(0.20)	2(0.20)	8(0.20)
Height (cm)			
N	3039	997	4036
Mean(SD)	162.65(9.23)	162.86(9.33)	162.70(9.26)
Median	163.00	162.50	162.80
Min, Max	137.00, 199.00	140.00, 193.00	137.00, 199.00
Weight (kg)			
N	3039	997	4036
Mean(SD)	62.61(13.74)	63.68(14.19)	62.87(13.86)
Median	60.00	61.00	60.00
Min, Max	32.30, 164.00	33.70, 140.50	32.30, 164.00
BMI (kg/m^2)			
N	3039	997	4036
Mean(SD)	23.59(4.35)	23.90(4.27)	23.67(4.33)
Median	23.00	23.50	23.10
Min, Max	13.20, 48.40	14.40, 45.10	13.20, 48.40

SD = standard deviation, Min = minimum, Max = maximum, BMI = body mass index. BMI (kg/m2) = weight (kg)/[height (cm)×0.01]^2.
Note: Denominator of percentage is the number of participants in each group.

Numbers analysed

The number and percentage of participants included in each analysis population is shown in Table 9.

Table 9. Analysis Sets (GBP510_003)

	GBP510 (N=3039)	**ChAdOx1-S (N=997)**	**Total (N=4036)**
Safety population	3029 (99.70%)	996 (99.80%)	4025 (99.73%)
Immunogenicity population (FAS)	1259 (41.55%)	628 (63.12%)	1887 (46.88%)
PPS1 for primary stage	877 (69.66%)	441 (70.22%)	1318 (69.85%)
CMI subset	76 (2.5%)	40 (4.01%)	116 (2.87%)

Outcomes and estimation

Primary outcome

GMTs

Two weeks after the second vaccination, the GMT adjusted for age group (18~64 years, ⩾65 years) and baseline antibody level was 272.1 IU/mL in GBP510 group [95% CI: 240.4, 308.0] and 92.8 IU/mL in ChAdOx1-S group [95% CI: 80.8, 106.5]. The GMT ratio of two groups was 2.9 [95% CI: 2.6, 3.3], p< 0.0001. The lower limit of two-sided 95% CI was 2.6, which was greater than Superiority margin of 1. Therefore, it was demonstrated that GMT of neutralising antibody responses against the parental D614G strain of GBP510 group was superior to ChAdOx1-S group.

Seroconversion rate

Two weeks after the second vaccination, the SCR was 98.1% (860/877 participants) in the GBP510 group [95% CI: 96.9, 98.9] and 87.3% (385/441 participants) in ChAdOx1-S group [95% CI:83.8, 90.3]. The difference between the two groups was 10.8% [95% CI: 7.7, 14.3], with a lower limit of the 95% CI greater than the predefined non-inferiority margin (-5.0%) (Table 10). Therefore, it was demonstrated that the SCR of neutralising antibody responses against the parental D614G strain of GBP510 group was non-inferior to ChAdOx1-S group.

Table 10. Immunogenicity Assessment by Wild-type Virus Neutralisation Assays (FRNT) at Visit 4 and 6 (Per-Protocol Set 1, GBP510_003)

		GBP510 (N=877)	**ChAdOx1-S (N=441)**
Baseline	n	877	441
	GMT	8.2	8.1
	95% CI	[8.1, 8.2]	[8.1, 8.2]
	Ratio of GMTs (GBP510 / ChAdOx1-S)	1.0	
	95% CI	[1.0, 1.0]	
Visit 4 (4 weeks after 1st vaccination) ‡	n	195	96
	Adjusted GMT†	11.0	40.4
	95% CI	[8.4, 14.3]	[30.5, 53.5]
	Ratio of GMTs (GBP510 / ChAdOx1-S)	0.3	
	95% CI	[0.2, 0.3]	
	GMFR (unadjusted)	1.4	5.1
	95% CI	[1.2, 1.6]	[4.0, 6.6]
	Participants with ≥ 4-fold rise, n(%)	11 (5.6)	54 (56.3)
	95% CI	[2.9, 9.9]	[45.8, 66.4]
Visit 6 (2 weeks after 2nd vaccination)	n	877	441
	Adjusted GMT†	272.1	92.8
	95% CI	[240.4, 308.0]	[80.8, 106.5]
	Ratio of GMTs ∗ (GBP510 / ChAdOx1-S)	**2.93**	
	95% CI	**[2.6, 3.3]**	
	P-value [2]	<0.0001	
	Lower Limit > 1	**Yes**	
	GMFR (unadjusted)	36.8	12.6
	95% CI	[34.6, 39.1]	[11.4, 13.8]
	Participants with ≥ 4-fold rise, n(%)	860 (98.1)	385 (87.3)
	95% CI	[96.9, 98.9]	[83.8, 90.3]
	Difference in % of the Participants with ≥ 4-fold rise ∗	**10.8**	
	95% CI	**[7.7, 14.3]**	
	P-value [3]	<0.0001 (c)	
	Lower Limit > -5%	**Yes**	

CI= Confidence Interval, GMT = geometric mean titre, GMFR = geometric mean fold rise, ANCOVA = analysis of covariance, NA = not applicable. Assay unit: IU/mL
[2] † ANCOVA model with treatment group, age group (18~64, ≥65) as factors, and baseline antibody level as covariate.
[3] Testing for difference between treatment groups (chi-square test (c) or Fisher's exact test (f)).
∗ = Co-primary Endpoint (superiority based on the 2-sided 95% CI of the ratio of post-vaccination GMT (GBP510 over ChAdOx1-S); non-inferiority based on the 2-sided 95% CI of the difference in the percentages of participants with ≥ 4-fold rise from baseline (GBP510 - ChAdOx1-S) in neutralisation antibody titre).
GMT = anti-logarithm[mean of natural logarithm(titre at visit n)], GMFR = anti-logarithm[mean of natural logarithm(titre at visit n/titre at visit 2)].
‡The test results are collected for randomly selected participants (about 20% of all participants) at Visit 4.
The 95% confidence intervals for GMT and GMFR are calculated using Wald method with t-distribution.
The 95% CI of percentage of participants ≥ 4-fold rises is calculated based on Clopper-Pearson method.
The 95% CI of the difference between groups is calculated based on Chan and Zhang method.
If ANCOVA model has infinite likelihood, ANCOVA under the assumption of homoscedasticity is used.

Secondary Outcomes

Neutralising antibody to the SARS-CoV-2 measured by wild-type virus neutralisation assay

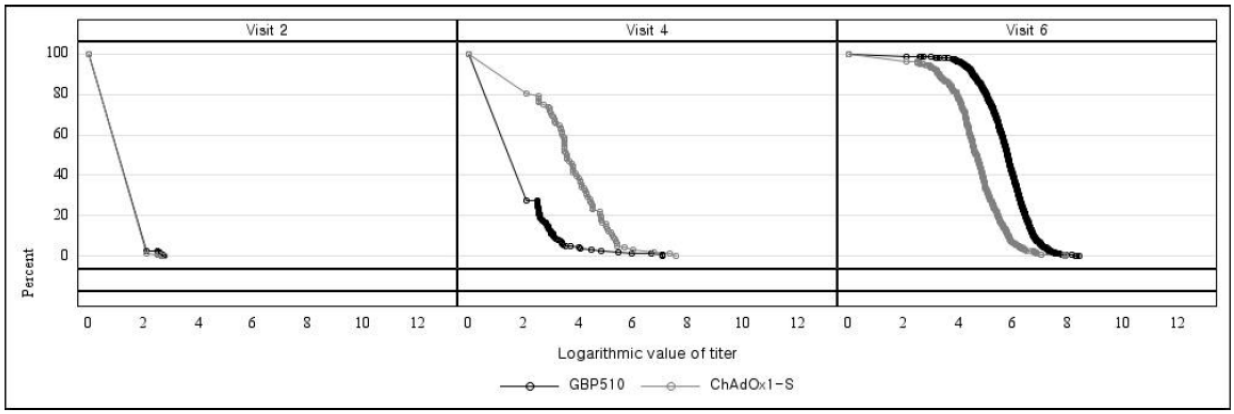
The GMTs, GMFR and proportion of participants with ⩾ 4-fold rise at 4 weeks post 1st vaccination and 2 weeks post 2nd vaccination are presented in Table 10.

On Visit 4 (4 weeks after 1st vaccination), GMT, GMFR, and proportion of participants with ⩾ 4-fold rise were higher in ChAdOx1-S group than in GBP510 group. The GMT ratio and seroconversion rate differences between two groups were statistically significant.

On Visit 6, GMT, GMFR, and proportion of participants with ⩾ 4-fold rise were higher in GBP510 group than in ChAdOx1-S group. GMT ratio and seroconversion rate differences between two groups were statistically significant.

The Reverse Cumulative Distribution Curves showing the responses at baseline (Visit 2), 4 weeks after the first dose (Visit 4) and 2 weeks after the second dose (Visit 6) are presented below in Figure 1.

Figure 1. RCDC for the Natural Logarithmic of Titre by Wild-type Virus Neutralisation Assays at Visit 2, 4, 6, Per-Protocol Set GBP510_003



SARS-CoV-2 RBD-binding IgG antibody measured by ELISA

A total of 877 participants in GBP510 group and 441 participants in ChAdOx1-S group were evaluated for SARS-CoV-2 RBD-binding IgG antibody by ELISA on baseline, Visit 4 and 6 in the PPS 1 (Table 11).

On both Visit 4 (4 weeks after 1st vaccination) and Visit 6 (2 weeks after 2nd vaccination), GMT, GMFR, and proportion of participants with ⩾ 4-fold rise were higher in GBP510 group than ChAdOx1-S group.

Table 11. Immunogenicity Assessment by ELISA at Visit 4 and 6 (Per-Protocol Set 1, GBP510_003)

	GBP510 (N=877)	**ChAdOx1-S (N=441)**
Baseline		
n	877	441
GMT	10.9	10.8
95% CI	[10.5, 11.3]	[10.3, 11.3]
Visit 4 (4 weeks after 1st vaccination)		
N	877	441
Adjusted GMT†	131.2	91.9
95% CI	[117.90, 146.09]	[81.55, 103.57]
GMFR	15.7	11.1
95% CI	[14.8, 16.8]	[10.1, 12.2]
Participants with ≥ 4-fold rise, n(%)	811 (92.5)	374 (84.8)
95% CI	[90.5, 94.1]	[81.1, 88.0]
Visit 6 (2 weeks after 2nd vaccination)		
N	877	441
Adjusted GMT†	2850.5	215.7

95% CI	[2586.5, 3141.3]	[193.5, 240.4]
GMFR	296.1	23.0
95% CI	[278.1, 315.2]	[21.1, 25.1]
Participants with ≥ 4-fold rise, n(%)	873 (99.5)	427 (96.8)
95% CI	[98.8, 99.9]	[94.7, 98.3]

CI=Confidence Interval, GMT = geometric mean titre, GMFR = geometric mean fold rise, ANCOVA = analysis of covariance. Assay unit: BAU/mL
† ANCOVA model with treatment group, age group (18~64, ≥65) as factors, and baseline antibody level as
GMT = anti-logarithm[mean of natural logarithm(titre at visit n)], GMFR = anti-logarithm[mean of natural logarithm(titre at visit n/titre at visit 2)].
95% confidence intervals for GMT and GMFR are calculated using Wald method with t-distribution.
The 95% CI of percentage of participants ≥ 4-fold rises is calculated based on Clopper-Pearson method.
The 95% CI of the difference in percentage of participants ≥ 4-fold rises between groups was calculated based on Wald method.

Cell-Mediated Immune Response

Cell-mediated Immune response (CMI) was assessed by FluoroSpot Assay and ICS assay to quantify cytokine secreting cells (Unit: SFC / 2.5 X 10^5 PBMCs) in a subset of 10% participants in Cohort 1 (Table 12).

Table 12. Cell-Mediated Immunity (ICS Assay) results in Phase III study GBP510_003 (Per-Protocol Set)

Time Point	Statistic	25 µg GBP510 + AS03		CHAdOx1-S	
		CD4+ T-cells	CD8+ T-cells	CD4+ T-cells	CD8+ T-cells
Cells expressing IFN-γ					
Baseline	n	70	70	36	36
	Mean [SD]	0.00 [0.01]	0.00 [0.01]	0.00 [0.00]	0.00 [0.00]
	Median [Min, Max]	0.00 [0.00, 0.05]	0.00 [0.00, 0.05]	0.00 [0.00, 0.02]	0.00 [0.00, 0.02]
2 weeks post-Dose 2	n	68	68	33	33
	Mean [SD]	0.01 [0.02]	0.01 [0.02]	0.00 [0.01]	0.01 [0.01]
	Median [Min, Max]	0.01 [0.00, 0.07]	0.00 [0.00, 0.15]	0.00 [0.00, 0.02]	0.01 [0.00, 0.06]
Cells expressing TNF-α					
Baseline	n	70	70	36	36
	Mean [SD]	0.24 [0.55]	0.04 [0.12]	0.11 [0.22]	0.04 [0.12]
	Median [Min, Max]	0.06 [0.00, 3.20]	0.02 [0.00, 0.88]	0.03 [0.00, 1.06]	0.02 [0.00, 0.73]
2 weeks post-Dose 2	n	68	68	33	33
	Mean [SD]	0.72 [1.11]	0.11 [0.26]	0.39 [0.72]	0.07 [0.13]
	Median [Min, Max]	0.23 [0.06, 4.58]	0.02 [0.00, 1.66]	0.09 [0.00, 3.12]	0.02 [0.00, 0.57]
Cells expressing IL-2					
Baseline	n	70	70	36	36
	Mean [SD]	0.02 [0.04]	0.00 [0.01]	0.01 [0.02]	0.00 [0.01]
	Median [Min, Max]	0.01 [0.00, 0.20]	0.00 [0.00, 0.05]	0.01 [0.00, 0.11]	0.00 [0.00, 0.06]
2 weeks post-Dose 2	n	68	68	33	33
	Mean [SD]	0.08 [0.08]	0.00 [0.01]	0.03 [0.05]	0.01 [0.01]
	Median [Min, Max]	0.06 [0.01, 0.48]	0.00 [0.00, 0.08]	0.02 [0.00, 0.24]	0.00 [0.00, 0.03]
Cells expressing IL-4					
Baseline	n	70	70	36	36
	Mean [SD]	0.00 [0.00]	0.01 [0.01]	0.00 [0.00]	0.01 [0.01]
	Median [Min, Max]	0.00 [0.00, 0.02]	0.00 [0.00, 0.07]	0.00 [0.00, 0.01]	0.00 [0.00, 0.04]
2 weeks post-Dose 2	n	68	68	33	33
	Mean [SD]	0.00 [0.00]	0.01 [0.01]	0.00 [0.00]	0.00 [0.01]
	Median [Min, Max]	0.00 [0.00, 0.02]	0.00 [0.00. 0.06]	0.00 [0.00, 0.01]	0.00 [0.00, 0.03]

Abbreviations: n = number of participants with available results in a specific time point; CI = confidence interval; SD = standard deviation; Min = minimum; Max = maximum.

Exploratory outcomes

Immunogenicity Assessment in Seropositive Participants

The participants with SARS-CoV-2 neutralising antibody (by FRNT) ⩾ LLOQ at baseline were evaluated by Neutralising antibody response against parental D614G strain by FRNT on baseline, Visit 4, and 6 in the FAS and the Visit 4 result was evaluated from approximately 20% of participants (Table 13).

Table 13. Neutralising Antibody Response in Seropositive Participants 1 by Wild-type Virus Neutralisation Assays (FRNT) Full Analysis Set

		GBP510 (N=1259)	**ChAdOx1-S** (N=628)
Baseline	Seropositive participants (%)	10.6%	10.5%
	n	133	66
	GMT	39.7	41.8
	95% CI	[33.4, 47.2]	[33.2, 52.7]
Visit 4 (4 weeks after 1st vaccination)	n	38	20
	GMT	329.4	339.8
	95% CI	[147.9, 733.6]	[162.9,708.7]
	Ratio of GMTs*	1.0	
	95% CI	[0.3, 2.8]	
Visit 6 (2 weeks after 2nd vaccination)	n	127	64
	GMT(SD)	989.6	473.6
	95% CI	[773.0, 1266.9]	[338.1,663.2]
	Ratio of GMTs *	2.1	
	95% CI	[1.4, 3.2]	

CI=Confidence interval, GMT = geometric mean titre, GMT = anti-logarithm[mean of natural logarithm(titre at visit n)].
*Ratio of GMTs GBP510 / ChAdOx1-S. Data Source: Listing 16.2.8.

Immunogenicity Assessment by Wild-type Virus Neutralisation Assays (FRNT50) against original strain, Delta and Omicron

Table 14. Immunogenicity Assessment by Live Virus Neutralisation Assays (FRNT50) against, Wildtype, Delta and Omicron at baseline (wildtype only) and visit 6 (Per-Protocol Set 1 GBP510_003)

		GBP510 (N=877)	**ChAdOx1-S (N=441)**
Wildtype			
Baseline	n	877	441
	GMT	21.6	21.3
	95% CI	[20.6, 22.7]	[19.8, 22.8]
	Ratio of GMTs	1.0	
	95% CI	[0.93, 1.11]	
Visit 6 (2 weeks after 2nd vaccination)	N	877	441
	GMT	1527.5	526.0
	95% CI	[1431.5, 1629.9]	[478.6, 578.0]
	Ratio of GMTs	2.9	

	95% CI	[2.6, 3.3]	
Delta*			
Visit 6 (2 weeks after 2nd vaccination	N	137	68
	GMT	2644.3	97.0
	95% CI	[2269.5, 3080.8]	[69.3, 135.7]
	Ratio of GMTs	27.3	
	95% CI	[18.9, 39.4]	
Omicron (BA.1)*			
Visit 6 (2 weeks after 2nd vaccination	N	137	68
	GMT	129.1	12.3
	95% CI	[107.4, 155.2]	[10.3, 14.6]
	Ratio of GMTs	10.5	
	95% CI	[8.2, 13.5]	

GMT = geometric mean titer, anti-logarithm[mean of natural logarithm(titre at visit n)].
*The test result was collected for subset of participants (about 10% of all participants).
95% confidence intervals for GMT and GMFR are calculated using Wald method with t-distribution.
The 95% CI of the difference between groups was calculated based on Wald method, 95% confidence intervals for GMT are calculated using Wald method with t-distribution.

Incidence rates of COVID-19

The incidence rates of virologically-confirmed COVID-19 case in each group was 2.1% of participants in GBP510 group and 3.3% in ChAdOx1-S group after any vaccination. After 14 days of 2nd vaccination, it was reported in 0.5% of participants in GBP510 group and 1.6% in ChAdOx1-S group.

The incidence rates of virologically-suspected COVID-19 case in each group was 1.6% of participants in GBP510 group and 1.1% in ChAdOx1-S group after any vaccination. After 14 days of 2nd vaccination, it was reported in 0.5% of participants in GBP510 group and 0.6% in ChAdOx1-S group.

All cases were reported as 'Asymptomatic' or 'Non-severe'.

Ancillary analyses

Subgroup Analysis by Age

A secondary objective of GBP510_003 was to assess the immune responses in seronegative adults 18-64 years of age and seronegative adults aged 65 years and older separately (Table 15).

In the age subgroup analysis of immunogenicity, distribution of age strata was balanced across groups. Among total of 1,318 participants in PPS1, 95.10% (834/877 participants) in GBP510 group and 94.56% (417/441 participants) in ChAdOx1-S group were aged between 18 to 64 years.

A total of 43 participants in GBP510 and 24 participants in ChAdOx1-S aged $\geqslant$ 65 years were evaluated for neutralisation antibody by FRNT on baseline, Visit 4 and 6 in the PPS1. Visit 4 assessment was conducted only in the subset population, comprised of approximately 20% of participants (8 participants from each group).

Table 15. Immune responses in seronegative adults 18-64 years of age and seronegative adults aged 65 years and older separately

		Age Group: 18-64 years		Age Group: ≥ 65 years	
		GBP510 (N=834)	**ChAdOx1-S (N=417)**	**GBP510 (N=43)**	**ChAdOx1-S (N=24)**
Baseline	n	834	417	43	24
	GMT	8.2	8.1	8.3	8.1
	95% CI	[8.1, 8.2]	[8.1, 8.2]	[8.0, 8.6]	[8.1, 8.1]
Visit 4 (4 weeks after 1st vaccination)	n	187	88	8	8
	Adjusted GMT†	11.5	40.8	8.1	49.8
	95% CI	[10.0, 13.2]	[33.2, 50.1]	[4.9, 13.4]	[30.2, 82.3]
	GMFR	1.4	5.0	1.0	6.2
	95% CI	[1.3, 1.6]	[3.9, 6.5]	[1.0, 1.0]	[2.8, 13.5]
	Participants with ≥ 4-fold rise, n (%)	11 (5.9)	49 (55.7)	0 (0.0)	5 (62.5)
	95% CI	[3.0, 10.3]	[44.7, 66.3]	[0.0, 36.9]	[24.5, 91.5]
Visit 6 (2 weeks after 2nd vaccination)	n	834	417	43	24
	Adjusted GMT†	304.3	103.2	235.8	87.3
	95% CI	[285.5, 324.4]	[94.2, 112.9]	[160.0, 347.7]	[51.7, 147.3]
	Ratio of GMTs (GBP510 / ChAdOx1-S)	2.96		2.63	
	95% CI	[2.64, 3.31]		[1.38, 5.02]	
	GMFR	37.3	12.7	28.3	11.1
	95% CI	[35.0, 39.6]	[11.5, 14.0]	[19.01, 42.16]	[6.47, 18.89]
	Participants with ≥ 4-fold rise, n (%)	819 (98.2)	366 (87.8)	41 (95.4)	19 (79.2)
	95% CI	[97.1, 99.0]	[84.2, 90.8]	[84.2, 99.4]	[57.8, 92.9]
	Difference in Proportions of the Participant with ≥ 4-fold rise	10.4		16.2	
	95% CI	[7.4, 14.1]		[-0.5, 37.6]	
	P-value [4]	<0.0001 (c)		0.0882 (f)	

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

Subgroup Analysis by Ethnicity

An exploratory objective of GBP510_003 was to describe the consistency of immunogenicity across ethnicities.

Table 16 shows the neutralising antibody titres (GMTs) either unadjusted, adjusted for age group and baseline antibody titre as covariate or adjusted for age group, sex and baseline antibody level as covariate.

Table 16. The Consistency among Ethnicities by Wild-type Virus Neutralisation Assay (FRNT) at visit 6 (per protocol set 1, GBP510_003)

		Korean		South East Asian		Caucasian	
		GBP510 (N=303)	**ChAdOx1-S (N=154)**	**GBP510 (N=529)**	**ChAdOx1-S (N=266)**	**GBP510 (N=45)**	**ChAdOx1-S (N=21)**
Baseline	n	303	154	529	266	45	21
	GMT	8.2	8.1	8.2	8.1	8.2	8.1
	95% CI	[8.1, 8.3]	[8.1, 8.2]	[8.1, 8.2]	[8.1, 8.2]	[8.0, 8.5]	[8.1, 8.1]
Visit 6 (2 weeks after 2nd vaccination)	n	303	154	529	266	45	21
	GMT	306.5	75.3	305.8	131.1	216.6	41.1
	95% CI	[280.8, 334.5]	[64.9, 87.3]	[281.1, 332.6]	[116.5, 147.6]	[152.3, 308.0]	[27.2, 62.2]
	Ratio of GMTs	4.1		2.3		5.3	
	95% CI	[3.4, 4.8]		[2.0, 2.7]		[3.0, 9.4]	
	GMFR	37.4	9.3	37.5	16.1	26.3	5.1
	95% CI	[34.2, 40.8]	[8.0, 10.7]	[34.44, 40.76]	[14.3, 18.2]	[18.3, 37.7]	[3.4, 7.7]
	Adjusted GMT†	528.3	129.9	268.7	115.9	154.4	28.1
	95% CI	[328.7, 849.2]	[80.1, 210.6]	[233.7, 309.0]	[98.6, 136.1]	[59.2, 402.8]	[10.3, 76.6]
	Ratio of GMTs	4.1		2.3		5.5	
	95% CI	[3.5, 4.8]		[2.0, 2.7]		[3.2, 9.4]	
	Adjusted GMT‡	522.6	128.5	270.1	116.0	144.7	27.8
	95% CI	[324.0, 842.8]	[79.0, 209.1]	[234.9, 310.7]	[98.7, 136.2]	[77.7, 269.5]	[14.1, 54.8]
	Ratio of GMTs	4.1		2.3		5.2	
	95% CI	[3.5, 4.8]		[2.0, 2.7]		[3.1, 8.9]	
	Participants with ≥ 4-fold rise, n(%)	301 (99.3)	124 (80.5)	518 (97.9)	249 (93.6)	41 (91.1)	12 (57.1)
	95% CI	[97.6, 99.9]	[73.4, 86.5]	[96.3, 99.0]	[90.0, 96.2]	[78.8, 97.5]	[34.0, 78.2]
	Difference in % ≥ 4-fold rise	18.8		4.3		34.0	
	95% CI	[12.5, 25.1]		[1.13, 7.49]		[11.23, 56.71]	

CI=Confidence Interval, GMT = geometric mean titer, GMFR = geometric mean fold rise, ANCOVA = analysis of covariance. Assay unit: IU/mL

† ANCOVA model with treatment group, age group (18~64, ≥65) as factors, and baseline antibody level as covariate.

‡ ANCOVA model with treatment group, age group (18~64, ≥65), sex as factors and baseline antibody level as covariate.

GMT = anti-logarithm[mean of natural logarithm(titer at Visit n)], GMFR = anti-logarithm[mean of natural logarithm(titer at visit n/titer at visit 2)]. 95% confidence interval for GMT and GMFR are calculated using t-distribution and Confidence Interval of Seroconversion rate is calculated using Wald method. 95% confidence interval for the percentage of participants ≥ 4-fold rises was calculated by Clopper-Pearson Methods. The 95% CI of difference in percentage of participants ≥ 4-fold rises between groups was calculated based on Wald method.

3.3.4.3. Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 17. Summary of efficacy for trial GBP510

Title: A Phase III, Randomised, Active-controlled, Observer-blind, Parallel-group, Multi-center Study to Assess the Immunogenicity and Safety of SK SARS-CoV-2 Recombinant Protein Nanoparticle Vaccine adjuvanted with AS03 (GBP510) in Adults Aged 18 Years and Older			
Study identifier	GBP510_003 / ClinicalTrials.gov identifier: NCT 05007951		
Design	Randomised, observer blinded, parallel group multicentre trial to compare the immunogenicity of GBP510 to ChAdOx1-S in adults (Cohort 1) and evaluate the safety of GBP510 (Cohort 2).		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 months not applicable not applicable
Hypothesis	Coprimary: Superiority (GMTs) and Non-inferiority (SCR) Superiority was achieved if the lower limit of the 2-sided 95% CI for the ratio of post-vaccination GMTs exceeded 1, and non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI for the difference of the percentage of participants with ⩾ 4-fold rise exceeded a non-inferiority margin of -5%.		
Treatments groups	SARS-CoV-2 Recombinant Protein Nanoparticle Vaccine with AS03 (GBP510)		GBP510 given as 2 doses (IM injection), with each dose containing 25 ug of SARSCoV-2 RBD nanoparticle with AS03 adjuvant, 28 days apart. 3039 randomised; 1259 in the full analysis set for Cohort 1 (immunogenicity)
	Chimpanzee Adenovirus encoding the SARS-CoV-2 Spike Glycoprotein (ChAdOx1-S)		ChAdOx1-S given as 2 doses (IM injection), with each dose containing 5×10^{10} , not less than $2.5x10^{8}$infectious units, 28 days apart. 997 randomised, 628 in the full analysis set for Cohort 1 (immunogenicity)
Endpoints and definitions	Co-Primary endpoint	GMT of neutralising antibodies at day 43	GMT of neutralising antibody to the SARS-CoV-2 measured by wild-type virus assay 2 weeks post 2^{nd} vaccination (FRNT)
	Co-Primary endpoint	Seroconversion of neutralising antibodies at day 43	Percentage of participants with ⩾ 4-fold rise in wild-type virus neutralising antibody titre from baseline to 2 weeks post 2nd vaccination (FRNT)
	Secondary endpoint	GMT, GMFR, & SCR of neutralising antibody to the	Immune response at 4 weeks after the 1st vaccination, and 2 weeks, 4 weeks, 6 months, and 12 months after the 2nd

		SARS-CoV-2 measured by FRNT	vaccination (Visit 4, 6, 7, 8, and 9) as determined by the GMT/GMFR, and % participants with ⩾ 4-fold rise of (SCR) of neutralising antibodies to the SARS-CoV-2 measured by wild-type virus assays (FRNT)
	Secondary endpoint	GMT, GMFR, SCR Of RBD-binding IgG antibody measured by ELISA	Immune response at 4 weeks after the 1st vaccination, and 2 weeks, 4 weeks, 6 months, and 12 months after the 2nd vaccination (Visit 4, 6, 7, 8, and 9) as determined by the GMT/GMFR, and % participants with ⩾ 4-fold rise of (SCR) of IgG antibodies to SARS CoV-2 S-protein as measured by ELISA
	Secondary endpoint	Cell-mediated response for both Th1 and Th2 cytokines	Cell mediated immune response at baseline and 2 weeks, 6 months, and 12 months after the 2nd vaccination (Visit 6, 8, 9) for both Th1 and Th2 cytokines measured by ELISpot and/or FluoroSpot, and for both CD4+ and CD8+ T-cells measured by FACS
Database lock	Database unlock was performed on 19 April 2022. Database lock for both Cohort 1 and 2 was performed on 20 April 2022.		

<u>Results and Analysis</u>

Analysis description	**Co-primary Analysis: SARS-CoV-2 Neutralising Antibody Titres**		
Analysis population and time point description	Per protocol set 1: all participants who completed the vaccination schedule, were not infected with SARS-CoV-2 and had no major protocol deviations (e.g. visit window deviation, blood sampling for immunogenicity not performed). A negative result in the immunoassay for the in vitro qualitative detection of antibodies to SARS-CoV-2 at Visit 6 was additionally required for PPS1. Determined at 14+-3 days after the second vaccination.		
Descriptive statistics and estimate variability	Treatment group	**GBP510**	**ChAdOx1-S**
	Number of subjects	877	441
	GMT	300.7	102.2
	95% CI	282.7, 319.8	93.0, 112.4
	SCR (%)	98.1	87.3
	95% CI	(96.9, 98.9)	[83.8, 90.3]
Effect estimate per comparison	Co-Primary endpoint	*Comparison groups*	GBP510/ChAdOx1-S
		GMT ratio	2.9
		95% CI	(**2.6**, 3.3)
		P-value (two sample t-test)	<0.0001
	Co-Primary endpoint	*Comparison groups*	GBP510/ChAdOx1-S
		Difference in SCR (%)	10.8

		95% CI	(**7.7**, 14.3)
Notes	*As the lower limit of two-sided 95% CI was 2.6, it was demonstrated that GMT of neutralising antibody responses against the parental D614G strain of GBP510 group was superior to ChAdOx1-S group. Further, the lower limit of 95% CI for the seroconversion difference was 7.7%, which was greater than the non-inferiority margin (-5.0%). It was demonstrated that the seroconversion rate of neutralising antibody responses against the parental D614G strain of GBP510 group was non-inferior to ChAdOx1-S group.* *Importantly, the presented analysis was not adjusted for stratification factors age and centre except for co-primary endpoint analysis of GMT.* Adjusted estimates of GMTs, and their associated 95% CIs were determined using analysis of covariance model with treatment group, age group (18~64, ≥ 65) as factors, and baseline antibody level as covariate.		

3.3.4.4. Clinical studies in special populations

See ancillary analysis.

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled Trials			
Non Controlled trials			

3.3.4.5. In vitro biomarker test for patient selection for efficacy

Not applicable.

3.3.4.6. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

3.3.4.7. Supportive study

Not applicable.

3.3.5. Discussion on clinical efficacy

Design and conduct of clinical studies

The Applicant is seeking approval of GBP510, a RBD nanoparticle protein-based AS03adjuvanted vaccine based on the parental D614G strain vaccine, for the following indication:

SKYCovion is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

The clinical development programme is based on an immunobridging strategy that compares the GBP510 vaccine with the authorised ChAdOx1-S vaccine for which efficacy has been established. No clinical efficacy studies were planned for GBP510 as these were considered not feasible. This was agreed by the CHMP in Scientific Advice (EMA/SA/0000062495).

Two ongoing clinical trials have been submitted in support of the application: the supportive Phase 1/2 trial GBP510_002 and the pivotal randomised controlled Phase 3 trial GBP510_003. Another Phase 1/2 trial, GBP510_001, which evaluated an alum adjuvanted version of GBP510 was submitted. As this study did not evaluate the to be marketed vaccine, which is to be given with the AS03 adjuvant, the data of this Phase 1/2 study are not considered relevant for this application.

According to the Applicant, all clinical trials are conducted in accordance with Good Clinical Practice Guidelines, and with all national and local requirements that were in place when the studies were conducted.

Dose finding study

Study GBP510_002 is a 3-stage, phase 1/2, placebo-controlled, randomised, observer-blinded, dose-finding study to assess the safety, reactogenicity, and immunogenicity of GBP510 adjuvanted with or without AS03 in healthy younger and older adults. This study was conducted in South-Korea.

Subjects were randomised to 2 IM injections of study vaccine or placebo at a 4-week interval. For stage 1, randomisation was at a 2:1:1 ratio to receive 10 µg GBP510 with or without AS03, 25 µg GBP510 with or without AS03, or placebo (normal saline). For stage 2, randomisation was at a 2:2:1:1 ratio to receive 10 µg GBP510 with AS03, 25 µg GBP510 with or without AS03, or placebo (normal saline); the 10 µg GBP510 group without AS03 was included only in Stage 1. Stage 3 is planned to evaluate a booster dose. These data were not yet available with the interim CSR. The Applicant is invited to submit an updated CSR including the data from stage 3 with the response to the LoQ. (OC)

The chosen endpoints are mostly in line with those of the Phase 3 trial and are considered adequate. Sampling time points seem to be reasonable and are assumed to appropriately allow evaluation of endpoints. The assays used to investigate immunogenicity endpoints in this study were, apart from the SARS-CoV2-IgG Enzyme Linked Immunosorbent Assay (ELISA) and the intracellular cytokine staining assay (ICS), not validated. This is acceptable for a supportive Phase 1/2 study. The assays used to measure neutralising antibody responses used in this study (PRNT and PBNA) were different from the assay used in the pivotal Phase 3 study (FRNT). This lowers the overall amount of support that can be provided by this study, but to inform dose decision this is not of concern. Of note, high level results from stage 3 have been included in the clinical summary of efficacy but were not included in the CSR. From this, it appears that a FRNT assay has been used to investigate the neutralising antibody response in this stage. It is expected that the Applicant clarifies whether all samples were reanalysed and how this post-hoc analysis was conducted. (OC)

Main study

GBP510_003 is a randomised active-controlled, observer-blind, multi-centre study to assess the immunogenicity and safety of SK SARS-CoV-2 recombinant protein nanoparticle vaccine adjuvanted with AS03 (GBP510) in adults aged 18 years and older. The study involved two cohorts. Cohort 1 (immunogenicity) includes only participants with no history of SARS-CoV-2 infection and COVID-19 vaccination confirmed by a SARS-CoV-2 rapid antibody kit at screening, for cohort 2 (safety) participants were enrolled regardless of their serostatus.

The trial included centres in six countries (South Korea, Philippines, Vietnam, Thailand, Ukraine, New Zealand). It is unclear whether and/or how the invasion of Russian forces in February 2022 impacted the centre(s) located in Ukraine and some discussion is requested. If there is relevant impact,

preferably the estimands framework is used to discuss this (EMA/214249/2022) (OC) Further, conflicting and incomplete information on the number of centres per country was found which needs to be clarified and corrected. (OC)

The study was conducted in healthy adults with no history of SARS-CoV-2 infection and COVID-19 vaccination confirmed by a SARS-CoV-2 rapid antibody kit. Serostatus at baseline is determined and the primary immunogenicity population should include seronegative persons only. Immunocompromised persons, persons with autoimmune disease and pregnant or breastfeeding women are excluded from this study. The in- and exclusion criteria also limited inclusion of people who had significant underlying comorbidities, or persons who were frail. Therefore the trial population is likely to reflect a healthy population. This limits conclusions regarding immunogenicity and safety in these subjects and it will need to be adequately reflected in the RMP.

Overall, the study objectives are considered appropriate for the intended purpose of immunobridging in adults. As has been discussed during scientific advice (EMA/SA/0000059587, May 2021), in absence of a generic ICP the choice of comparator is highly relevant. ChAdOx1-S was considered an acceptable comparator in scientific advice (EMA/SA/0000059587, May 2021). As the platform between GBP510 and ChAdOx1-S differ, it was agreed that the Applicant will need to demonstrate that GBP510 elicits higher neutralising antibody titres 2 weeks after the second dose compared to ChAdOx1-S and that the seroconversion rates should not be lower in individuals vaccinated with GBP510 compared to individuals vaccinated with ChAdOx1-S.

As discussed during scientific advice, there is a possibility that the immune response of the two vaccines are not compared at their peak and the comparison is favourable to GBP510. This doubt remains and the Applicant is asked to provide comparative results at 4 weeks post 2nd dose (this analysis is planned as secondary objective/endpoint and the data is expected to be available) (OC).

The co-primary objectives were in line with this advice. The study aimed to demonstrate that the immune response induced by 2 doses of GBP510 25µg adjuvanted to AS03 at 4-week interval in seronegative adults aged 18 years and older is both superior with regard to GMT ratio's and non-inferior to the immune response (seroconversion rate) induced by 2 doses of ChAdOx1-S. Immunobridging was based on neutralising antibodies as measured by the FRNT assay (see PD section). The (co)primary statistical hypotheses specified for the primary objectives were agreed upon as part of Scientific Advice (EMA/SA/0000062495, June 2021).

The secondary endpoints cover a broad characterisation of the immune response, including CMI and are agreed. As an exploratory endpoint, incidence rates of virologically-confirmed COVID-19 between Test group and Control group were compared. There is however only very limited information provided on how COVID-19 cases would be collected, how information on COVID-19 cases would be collected, how cases were classified as being symptomatic or asymptomatic, how testing was performed. This need to be further detailed. (OC)

The phase III study was observer-blind study. The appearance of GBP510 and ChAdOx1-S are different and the Applicant should clarify how blinding was ensured. (OC)

For GMT (first primary endpoint), hypothesis testing will be performed to assess superiority based on the 2-sided 95% CI of the ratio of post-vaccination GMT 2 weeks post 2nd vaccination (GBP510 over ChAdOx1-S) using 2-sided CIs at 0.05 significance level. Adjusted estimates of GMTs, and their associated 95% CIs were determined using analysis of covariance model with treatment group, age group (18~64, ≥65) as factors, and baseline antibody level as covariate. The ANCOVA model was fitted to the log-transformed value, then back to the original scale for presentation. The per protocol set 1 was used for the primary analysis, which was accepted. Missing data is not imputed. Post-randomisation imbalances will be assessed, as differential drop-out between the arms may impact the

outcome. Given the primary analysis will be performed in seronegative subjects, the Applicant is asked to clarify the rational to adjust for baseline (OC). In addition, as randomisation has been stratified for centre, the Applicant is asked to present the randomisation list and the results with the addition of adjustment by centre, or provide a justification why adjustment was not performed (EMA/CHMP/295050/2013) (OC).

For seroconversion (second co-primary endpoint) hypothesis testing will be performed to assess non-inferiority based on the 2-sided 95% CI of the difference in the percentages of participants with ≥ 4-fold rise from baseline to 2 weeks post 2nd vaccination (GBP510 - ChAdOx1-S) in neutralisation antibody titer, using 2-sided CIs at 0.05 significance level. Non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI for the difference of the percentage of participants with ≥ 4-fold rise exceeded a non-inferiority margin of -5%. The per protocol set 1 was used for the primary analysis, missing data is not imputed. Post-randomisation imbalances will be assessed, as differential drop-out between the arms may impact the outcome.

For exploratory analysis, the Applicant is requested to provide more information on the definition false negative results of SARS-CoV-2 antibody test at screening and present an overview of these results per treatment group (OC).

Planned subgroups are age group (18-64 years, ≥ 65years), sex (Male, Female), and race (Asian, Caucasian).

Immunogenicity data and additional analyses

Dose-finding study

A total of 328 people were randomised and received at least a first dose. Higher neutralising antibody titers and seroconversion rates were observed in the GBP510 25 ug with AS03 group when compared to the non-adjuvanted groups or GBP510 10 ug with AS03 group at two and four weeks after Dose 2 (visit 6 and 7, respectively).

The response 4 weeks after the second dose (visit 7) is already substantially lower than the response 2 weeks earlier (at visit 6). This is observed both for binding antibodies (GMT 1943 vs. 2599) as well as for neutralising antibodies (GMT 1107 vs. 1431), and for all vaccine formulations. The Applicant is invited to submit available immunogenicity data at later timepoints (e.g. visit 8 and further) in order to get a better understanding of the kinetics of the GBP510 induced immune response. (OC)

Cell mediated immunity was assessed in a subset of participants using an intracellular cytokine staining assay (ICS) which was validated according to the Applicant. This is not agreed, as several other concerns are raised regarding the validation exercise (see PD). The CMI results should hence be considered preliminary. Overall, T-cell responses were generally low but appeared Th1 skewed.

Taken together, the provided data support the selection of GBP510 25 µg adjuvanted with AS03 for the phase 3 study. Highest responses were observed in the adjuvanted groups when compared with the non-adjuvanted groups at two and four weeks after Dose 2, and all point estimates for the 25 µg + AS03 group were higher for both IgG and neutralising antibodies as compared to the 10 µg + AS03 group. Further, although the 25 µg+AS03 group reported most reactions the difference with the 10 µg + AS03 group is limited and the reactogenicity profile appears acceptable.

Main study

In Cohort 1 and Cohort 2 combined, a total of 4,913 subjects were screened and 4,036 were randomised to receive GBP510 or ChAdOx1-S. The majority of screen failures was reported with reason "Other" (n=457, 52%) without further specification. The Applicant should provide further information. (OC) In addition, it is noted that only 7 screening failures occurred in the Korean population, 808 in the

Southeast Asian population, and 60 in the Caucasian population. The Applicant is asked to explain the large difference in the percentage screen failures between those populations (OC).

The first participant was enrolled 30 August 2021, the last participant had its visit 7 (4 weeks after the second dose) 18 March 2022. The SAP was finalised on 11 April 2022, which appears just before the interim database lock of April 20. However, the Applicant also refers to a partial database lock on April 9 for the interim analysis. Therefore, it is unclear whether the SAP was indeed finalised before any unblinding of the data. This should be clarified by the Applicant (OC).

An overview of the number of participants randomised per centre and per country is requested. (OC)

The protocol was updated 3 times. Protocol changes version 1.2 (d. 3-9-2021) and 1.3 (d. 21-02-2022) were introduced after enrollment had started. The majority of changes introduced in these versions are not expected to affect the enrolled study population, primary analysis or impact conclusions. A major change in version 1.2 was, according to the Protocol Amendment Summary of Changes Table, that *The rapid antibody kit test against SARS-CoV-2 has been replaced with the in vitro qualitative immunoassay*. The exact change is not understood as also in later versions of the protocol, screening at baseline seems to have been done with a rapid antibody kit, whilst at visit 6 an in vitro qualitative immunoassay seems to have been introduced. The Applicant should clarify this change in the protocol, clarify how this affected the PPS-1 analysis population, and provide details on the in vitro qualitative immunoassay used. (OC)

In total, 550 subjects (13.6%) had 968 major protocol deviations. Major protocol deviations seem to be balanced across groups. The definition of what constitutes a major protocol deviation was rather loose, and there are several examples of deviations which were labelled major, however are not impactful on the efficacy assessments and would therefore normally not result in an exclusion from the PP population. For example, "CMI sample stored in wrong temperature and discarded" was a reason for exclusion from the PPS1 population, but CMI is not part of the primary endpoint analysis and CMI material was only collected in a small subset of participants.

Participants who had a history of SARS-CoV-2 infection confirmed by medical interview, a FRNT value above LLOQ at baseline or participants who were positive for SARS-CoV-2 Ab N-protein test at baseline and/or Visit 6 were not included in the PPS1 analysis population. This is appropriate.

The Applicant only provided demographics and baseline characteristics for the ITT population and these should be provided for the FAS and PPS1 analysis populations as well (OC). In the ITT dataset, the intervention arm and control arm were comparable with regard to age at randomisation, ethnicity, sex, height, weight and BMI. Comorbidities were few, reflecting a healthy study population, and balanced between the treatment group.

Primary analysis

Overall, 1318 participants were included in the PPS1 analysis population, 877 subjects in the GBP510 group and 441 participants in the ChAdOx1-S group. Both co-primary endpoints were met in this population. GMT of neutralising antibody to the SARS-CoV-2 measured by wild-type virus neutralisation assays 2 weeks post 2nd vaccination was 272 (95%CI: 240, 308) in the GBP510 group vs. 93 (95%CI: 81, 106) in the control arm. The neutralising antibody GMT ratio (95% CI) was 2.9 (2.6, 3.2). This was based on a (prespecified) analysis adjusted with treatment group and age group (18~64, ⩾65) as factors, and baseline antibody level as covariate. Superiority for GBP510 compared to ChAdOx1-S for the neutralising GMTs can be concluded.

The percentage of participants with ⩾ 4-fold rise in wild-type virus neutralising antibody titre from baseline to 2 weeks post 2nd vaccination was 98.1% and 87.3% in the intervention and control arm, respectively. The seroconversion rate difference between two groups was 10.76% [95% CI: 7.68,

14.32]. The lower limit of the 95% CI for the difference was greater than the non-inferiority margin (-5.0%) thus non-inferiority can be concluded for the SCR.

Therefore, in principle efficacy can be inferred.

Given the primary analysis was prespecified to be performed in seronegative subjects, it is not understood why adjustment for baseline was planned as the primary analysis. Clarifications are requested. Further, a sensitivity analysis is requested in which the GMTs are adjusted for age group and centre (OC). In addition, the Applicant should repeat the analysis of both primary endpoints based on a subset of the FAS that only excludes subjects who meet the definition of a confirmed infection at baseline or during the primary stage of the study (i.e. without excluding subjects due to protocol deviations) (OC).

The peak of the immune response for GBP510 was at 2 weeks after the 2nd vaccination and it declines at 4 week. There is a likelihood that the immune response of the two vaccines are not compared at their peak favouring GBP510, this was discussed during scientific advise, and for the primary analysis accepted. However, the Applicant is asked to provide comparative results at 4 weeks post 2nd dose (this analysis is planned as secondary objective/endpoint and the data is expected to be available) (OC).

Response after first dose, binding antibody response

Secondary endpoints included the neutralising antibody response after a first dose as well as the binding antibody response measured by ELISA.

The neutralising antibody response is limited four weeks after the first dose of GBP510 (adj. GMT=11, 95%CI: 8-14) and reduced compared to ChAdOx1-S (adj. GMT=40, 95%CI: 30-54), clearly pointing out that the second dose of GBP510 is necessary for adequate priming. In contrast to the neutralising antibody response, the binding antibody response is much more prolific after the first dose in the GBP510 arm. The GMTs of RBD IgG measured by ELISA were higher 4 weeks after the first dose in the GBP510 arm (GMT=172, 95%CI: 163, 18) compared to the ChAdOx1-S arm (119, 95%CI: 110, 130). This suggests that the correlation between the ELISA and neutralisation assay is different in the two vaccine groups.

The Applicant is asked to present the neutralising antibody results as well as the binding antibody results for the FAS (cohort 1) and ITT (cohort 1) in overview tables. (OC)

The seroconversion rates as seen in the ChAdOx1-S arm are in line with the % with four-fold rise observed in the trials underpinning licensure for ChAdOx1-S (vaxzevria-previously-covid-19-vaccine-astrazeneca-epar-public-assessment-report_en.pdf (europa.eu), tables 9 and 10). The Applicant is, in addition, asked to present the neutralising antibody results as well as the binding antibody results for the FAS (cohort 1) and ITT (cohort 1). The Applicant is requested to present the % responders according to 2-fold rise and 10-fold rise for both arms at both timepoints (visit 4, visit 6). (OC) Further, it would be highly appreciated if assay results are calibrated according to the WHO international standard. (OC, also see PD) The RCDCs however seem reassuring.

Variants of Concern

Unexpected findings are also observed in relation to the neutralising antibody response towards the Delta (B.1.617.2) and Omicron (B.1.1.529) variant strains. It is unclear which sublineage of omicron was used in the assay, this should be clarified (OC). The Applicant is requested to clarify the validation status of both assays (OC). Finally, the Applicant is requested to inform on the plans and progress made so far with respect to the testing of neutralising activity against currently circulating Variants of Concern. Any available data should be shared (OC).

Responses were evaluated in a subset of participants (n=137 participants (15.6%) in the GBP510 group and n=68 participants (15.4%) in the ChAdOx1-S group), with unvalidated FRNT assays. It is unclear how this subset was selected, and this should be clarified. (OC) Also, baseline titres were not presented and are requested. (OC) The data are suggestive of a higher neutralising antibody (FRNT50) response against delta and omicron by GBP510 compared to ChAdOx1-S. However, there is an unexpected substantially higher response against the delta strain (GMT=2644) compared to the original strain (GMT=1527) in the GBP510 arm, which is not observed in the control arm (GMT=525 against the original strain, GMT=97 against Delta). Therefore, the Applicant should first and foremost confirm that the readouts are correct. (OC) If the readouts are correct, the divergent relative response between the two vaccine groups should be explained. (OC) Lastly, it would be helpful if the results against the original strain at available timepoints would be provided for the same subgroup of 137 and 68 individuals for which the neutralising antibody response against delta and omicron have been determined. (OC)

Response in seropositive persons

The neutralising antibody response in participants seropositive at baseline shows a similar pattern after the first dose in both groups, with an approximately 7-fold increase in titres in both the GBP510 group and the ChAdOx1-S group. Following a second dose a further increase is seen in both groups, albeit stronger in the GBP510 arm compared to the ChAdOx1-S group. The further increase is not fully expected considering the population (seropositive) and data in the ChAdOx1-S dossier that show a plateau in the neutralising antibody response after the first dose in persons with measurable neutralising antibodies at baseline [in seropositive persons who received 2 standard doses of ChAdOx1-S, the GMT post dose 1 was 1651 (95% CI: 1032.98, 2640.87), the GMT post dose 2 was 919.41 (95% CI: 597.78, 1414.11). A similar pattern was observed for the binding antibody response, with higher titres post dose 1 compared to post dose 2. (see: vaxzevria-previously-covid-19-vaccine-astrazeneca-epar-public-assessment-report_en.pdf (europa.eu), table 6). Due to the low number of samples at D29, it is unlikely that any further analysis can elucidate what is the reason behind this observation. Hence this is not further pursued.

The Applicant explains that the sero-status at baseline was based on the FRNT assay. There are some discrepancies between the numbers of sero-positive subjects analysed and reported in tables 51 and 52 and respectively the numbers reported in Figure 3 of the interim CSR. These discrepancies should be explained or corrected. (OC)

Subgroup analyses

The Applicant presented the results of the subgroup analyses by age and ethnicity. The Applicant is requested to also discuss the results of the subgroup analysis of the neutralising antibody responses by sex (M/F) and summarise in an overview table. (OC)

There were only 43 participants in the GBP510 group and 24 participants in ChAdOx1-S group aged ≥ 65 years of age for whom neutralising antibody titres were determined (FRNT). The pattern was consistent with what was observed in the overall population, which is reassuring. The absolute response in the older adults is slightly reduced compared to the response observed in the younger adults in both treatment groups. The clinical relevance of this difference remains unknown. Given that it has been demonstrated that ChAdOx1-S is efficacious in older adults (albeit during earlier pandemic waves), it is reasonable to expect at least a similar level of protection afforded by GBP510 against symptomatic SARS-CoV-2 infection in older adults aged 65 years or older.

The subgroup analysis by ethnicity (Korean, Southeast Asian, Caucasian) revealed some unexpected observations. The Applicant suggests that as two weeks after the second dose the titres are higher in the GBP510 group compared with the ChAdOx1-S group in each subgroup, the results are consistent

between these three subgroups. However, whilst the same conclusion of efficacy may be reached for each subgroup the magnitude of the responses between the three subgroups do not seem consistent, there seems to be a quantitative interaction between treatment and ethnicity. For example, there is a larger variation in responses (unadjusted analyses) in the ChAdOx1-S arm between the three ethnic groups as compared to the variation observed in the GBP510 arm. For example, the GMFRs in the ChAdOx1-S arm in the Southeast Asian and Korean subgroup are 16 and 9 respectively, the GMFR is 37 for both subgroups in the GBP510 arm. The SCR at visit 6 in the ChAdOx1-S arm is 57% in Caucasians, 81% in Koreans and 94% in Southeast Asians; the SCR in the GBP510 arm at the same timepoint is 91%, 99% and 98% respectively. Not surprising, the difference in SCR between the arms differ substantially for the three subgroups. Questions are raised to further understand the observed variation in the two treatment arms across the subgroups. (OCs).

Further, there is a large difference between the adjusted and unadjusted analyses in the Korean and Southeast Asian subgroup; whilst the unadjusted GMTs are similar between the two groups, the adjusted GMTs are substantially higher in the Korean subgroup but lower in the Southeast Asian subgroup. Also here, questions are asked to further elucidate this observation. (OCs)

The response in Caucasian participants appear consistently lower in both treatment groups (with GMTs of 217 and 41 in the GPB510 and ChAdOx1-S group respectively), as compared to the other ethnic subgroups (e.g. GMTs >300 for GBP510 and 75/131 for ChAdOx1-S in Korean/Southeast Asian participants respectively).

As the data suggest considerable variation in response between ethnicities – and this appears to affect the response in the two treatment groups differently, the relevance of the data for the European population is not self-evident and the Applicant should provide a justification for extrapolation of these results to the European population (OC).

CMI

Cell-mediated immunity was assessed in a pragmatically selected subgroup of participants, which is acceptable considering it is a descriptive analysis. Both a FluoroSpot assay as well as intracellular cytokine staining (ICS) was used. Although the Applicant states these assays were validated, several other concerns are raised (see PD) and the validation status is not agreed with. Therefore, all CMI results should be considered preliminary. Overall, CMI responses are low, and no clear differences are observed between the two vaccine groups. There are in both assays numerical differences for some of the measured Th1 cytokines between the 2 vaccine groups, but these seem to be largely due to differences that are already present at baseline, and no consistent pattern is observed. The presented results therefore do not suggest a major difference in the induced T-cell response between the two vaccines, but are reassuring in so far that none of the 2 vaccines induced a Th2 response.

Incidence rates of COVID-19

Incidence rates of virologically confirmed COVID-19 cases for both study arms have been provided as an exploratory objective. These are of interest as they may support the immunobridging exercise. However, as it is currently unclear how cases and information around cases was collected, the reliability of these data cannot be determined. Information is requested on how cases were distributed over follow up time in both study arms. Further, information on how cases were distributed between centres and between regions should be provided. Finally details should be provided on the number of suspected cases that had a negative SARS-COV-2 test for both study arms. (OC) In addition, the Applicant should provide a more detailed analysis of Covid breakthrough cases by age, ethnicity, comorbidity, and risk factors (OC). Information on the variants circulating at the time of the study in the regions were the study was conducted is expected (OC).

Additional efficacy data needed in the context of a Conditional MA

The Applicant has requested to be granted a Conditional Marketing Authorisation (CMA) for GBP510 adjuvanted with AS03 subject to specific obligations in accordance with Article 14(7) of Regulation (EC) No 726/2004. As stated by the Applicant in their justification document, comprehensive data, including results from non-clinical and clinical studies, are included in this CMA submission. The studies are ongoing and further data will become available in the coming months. It is, however, agreed with the Applicant that the data already available in the dossier can be considered comprehensive and if all concerns can be resolved a full MA would be appropriate.

3.3.6. Conclusions on clinical efficacy

GBP510 was shown to be immunogenic in studies GBP510_002 and _003. In pivotal study 003, both co-primary endpoints were met; therefore, efficacy can be inferred in principle.

Due to some uncertainty around the responses observed in the control arm, and unexpected observations in subgroup analyses which cannot easily be explained at this moment, several OCs are raised that need to be answered satisfactorily in order to get a better understanding of the data, and it's reliability before a final conclusion can be drawn.

The following measures are necessary to address the missing efficacy data in the context of a future Conditional MA:

None

3.3.7. Clinical safety

The clinical safety of GBP510 has been evaluated in two clinical trials: a phase 1/2 first in human dose-finding trial, GBP510_002, and the pivotal phase 3 trial, GBP510_003. The Applicant has presented pooled safety data from the GBP510_002 and GBP510_003 studies.

Safety methods

Apart from clinical laboratory evaluations, which were only done in GBP510_002, the methods for collection of safety data were similar for both studies _002 and _003.

All participants will be kept under observation for at least 30 minutes after each vaccination to ensure their safety. During this period, any unsolicited AEs will be recorded as 'immediate systemic reactions', whilst solicited and unsolicited local and systemic reactions will be recorded as any other reactions.

The following **solicited AEs** were collected for days 0 (vaccination day) to day 6 inclusive:

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

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.

Solicited AEs beyond 7 days after vaccination were reported in the eCRF.

Unsolicited AEs were recorded 28 days after each vaccination on a paper diary card. In the case of SAEs, MAAEs and AESIs, relevant information will be collected and assessed throughout the study,

from the 1st study vaccination (Day 0) until 12 months after the last study vaccination (Day 365±14 after Visit 4).

All SAEs were to be documented and reported, regardless of a causal relationship.

An MAAE is an AE that leads to hospitalisation, emergency room visits, or otherwise an unscheduled visit to a healthcare professional for any reason.

A list of AESI was defined according to Brighton Collaboration: COVID-19 Adverse Events of Special Interest list, in addition to a list of potential immune-mediated diseases (pIMDs). 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 aetiology.

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 aetiologies 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 to be related to the study intervention.

3.3.7.1. Patient exposure

The safety database includes 3133 subjects who received the GBP510 25 µg adjuvanted with AS03 vaccine candidate (1 squalene (10.69 milligrams), DL-α-tocopherol (11.86 milligrams) and polysorbate 80 (4.86 milligrams)). These subjects were included in 2 clinical trials, GBP510_003 (n=3,029) and GBP510_002 (n=104).

Table 18. Exposure in GBP510_003 and GBP510_002

	GBP510_003			**GBP510_002**	
	GBP510	ChAdOx1-S	Total	GBP510 25 µg + AS03	Placebo
Randomised	3039	997	4036	104	61
Received 1st dose	3030 (99.7%)	995 (99.8%)	4025[1](99.7%)	104 (100%)	61 (100%)
Received 2nd dose	2900 (95.4%)	958 (96.1%)	3858 (95.6%)	103 (99%)	60 (98.4%)

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

Baseline characteristics for subjects in the pooled data set are presented in Table 19.

Table 19. Demographics (Safety Set Pooled Data)

	GBP510 25ug+AS03 N=3133 from 002 (N=104) and 003 (N=3029)	ChAdOx1-S N=996 from 003	Placebo N=61 from 002
Age (years)			
N	3133	996	61
Mean ± SD	37.98 ± 13.86	39.33 ± 13.80	43.28 ± 14.68
Median	37.00	38.00	42.00
Min, Max	18.00, 88.00	18.00, 87.00	19.00, 80.00
Age group, n (%)			
18~64 years	2,963 (94.57)	942 (94.58)	56 (91.80)
≥ 65 years	170 (5.43)	54 (5.42)	5 (8.20)
Sex, n (%)			
Male	1,852 (59.11)	572 (57.43)	26 (42.62)
Female	1,281 (40.89)	424 (42.57)	35 (57.38)
Race, n (%)			
Asian	2,953 (94.25)	930 (93.37)	61 (100.00)
Korean	431 (13.76)	168 (16.87)	61 (100.00)
Southeast Asian	2,521 (80.47)	761 (76.41)	0 (0.00)
Caucasian	174 (5.55)	64 (6.43)	0 (0.00)
Black	0 (0.00)	0 (0.00)	0 (0.00)
Hispanic	0 (0.00)	0 (0.00)	0 (0.00)
Other	6 (0.19)	2 (0.20)	0 (0.00)

Note: SD: Standard deviation, Min: Minimum, Max: Maximum; %: n / (No. of subject in Safety Set by group) × 100
The number of participants for safety set were displayed according to actual treatment group. One participant in GBP510_003 study was administered incorrect IP inconsistent (ChAdOx1-S) with randomisation assignment (GBP510 25ug+AS03) Abbreviations: AS03 = Adjuvant system 03; SD = standard deviation; Max = Maximum; Min = Minimum; n = number of subjects in group; N = Number of subjects.

3.3.7.2. Adverse events

Table 20. Overview of Solicited AEs, SAEs, MAAEs and AE Leading to Early Study Termination (Safety Set Pooled Data)

	GBP510 25ug+AS03 N=3133 from 002 (N=104) and 003 (N=3029)	Placebo N=61 from 002	ChAdOx1-S N=996 from 003
Adverse Events after any vaccine injection			
Immediate AEs, n(%) [95% CI]			
Immediate unsolicited AEs	6 (0.19) [0.07, 0.42]	0 (0.00) [0.00, 5.87]	0 (0.00) [0.00, 0.37]
Immediate unsolicited ADRs	5 (0.16) [0.05, 0.37]	0 (0.00) [0.00, 5.87]	0 (0.00) [0.00, 0.37]
Solicited reaction within 7 days after vaccination, n(%) [95% CI]			
Solicited Local AEs	1813 (57.87) [56.12, 59.60]	13 (21.31) [11.86, 33.68]	490 (49.20) [46.05, 52.35]
Solicited Systemic AEs	1640 (52.35) [50.58, 54.11]	35 (57.38) [44.06, 69.96]	533 (53.51) [50.36, 56.65]
Solicited Local AEs (≥Grade 3)	59 (1.88) [1.44, 2.42]	0 (0.00) [0.00, 5.87]	6 (0.60) [0.22, 1.31]
Solicited Systemic AEs (≥Grade 3)	166 (5.30) [4.54, 6.14]	1 (1.64) [0.04, 8.80]	61 (6.12) [4.72, 7.80]
Within 28 days after vaccination, n(%) [95% CI]			
Unsolicited AEs	421 (13.44) [12.26, 14.68]	10 (16.39) [8.15, 28.09]	145 (14.56) [12.43, 16.90]
Unsolicited ADRs	111 (3.54) [2.92, 4.25]	2 (3.28) [0.40, 11.35]	41 (4.12) [2.97, 5.54]
Unsolicited severe AEs (≥Grade 3)	22 (0.70) [0.44, 1.06]	0 (0.00) [0.00, 5.87]	12 (1.20) [0.62, 2.10]
Unsolicited severe ADRs (≥Grade 3)	4 (0.13) [0.03, 0.33]	0 (0.00) [0.00, 5.87]	2 (0.20) [0.02, 0.72]
SAEs, n(%) [95%CI]	16 (0.51) [0.29, 0.83]	0 (0.00) [0.00, 5.87]	7 (0.70) [0.28, 1.44]
AESIs, n(%) [95%CI]	2 (0.06) [0.01, 0.23]	0 (0.00) [0.00, 5.87]	1 (0.10) [0.00, 0.56]
MAAEs, n(%) [95%CI]	156 (4.98) [4.24, 5.80]	4 (6.56) [1.82, 15.95]	50 (5.02) [3.75, 6.57]
MAADRs, n(%) [95%CI]	19 (0.61) [0.37, 0.95]	1 (1.64) [0.04, 8.80]	10 (1.00) [0.48, 1.84]
AEs leading to early study termination, n(%) [95% CI]	3 (0.10) [0.02, 0.28]	0 (0.00) [0.00, 5.87]	2 (0.20) [0.02, 0.72]
AEs leading to death, n(%) [95% CI]	0 (0.00) [0.00, 0.12]	0 (0.00) [0.00, 5.87]	1 (0.10) [0.00, 0.56]

Note: %: n / (No. of subject in Safety Set by group) * 100; The number of participants for safety set were displayed according to actual treatment group. One participant in GBP510_003 study was administered incorrect IP inconsistent (ChAdOx1-S) with randomisation assignment (GBP510 25ug+AS03). Confidence Interval for the percentage of subjects with AE is calculated by Clopper-Pearson Methods. * The case checked on 'at the discretion of the investigator or sponsor due to safety concerns' as a primary reason for discontinuation and checked on 'Stop Vaccination (only if, prior to 2nd vaccination)' as changes to IP vaccination. Abbreviations: AS03 = Adjuvant system 03; AEs = Adverse Events, MAAEs = Medically Attended Adverse Events; SAEs = Serious Adverse Events Source: Pooled Data Tables for Safety

Solicited Local Adverse Events

Solicited local AEs occurring within 7 days following each vaccination by severity are presented in Table 21.

Table 21. Solicited Local Adverse Events, Following each Vaccination, by Severity (Safety Set)

	GBP510 25ug+AS03 N=3133 from 002 (N=104) and 003 (N=3029)	Placebo N=61 from 002	ChAdOx1-S N=996 from 003
Solicited Local AEs after any vaccine injection, n(%)			
Injection Site Pain			
Grade 1 (Mild)	1419 (45.29)	13 (21.31)	414 (41.57)
Grade 2 (Moderate)	317 (10.12)	0 (0.00)	66 (6.63)
Grade 3 (Severe)	47 (1.50)	0 (0.00)	6 (0.60)
Grade 4 (Life Threatening)	0 (0.00)	0 (0.00)	0 (0.00)
Injection Site Redness			
Grade 1 (Mild)	107 (3.42)	0 (0.00)	20 (2.01)
Grade 2 (Moderate)	52 (1.66)	0 (0.00)	0 (0.00)
Grade 3 (Severe)	11 (0.35)	0 (0.00)	0 (0.00)
Grade 4 (Life Threatening)	0 (0.00)	0 (0.00)	0 (0.00)
Injection Site Swelling			
Grade 1 (Mild)	132 (4.21)	0 (0.00)	11 (1.10)
Grade 2 (Moderate)	46 (1.47)	0 (0.00)	1 (0.10)
Grade 3 (Severe)	4 (0.13)	0 (0.00)	0 (0.00)
Grade 4 (Life Threatening)	0 (0.00)	0 (0.00)	0 (0.00)
Solicited Local AEs after 1st vaccine injection, n(%)			
Injection Site Pain			
Grade 1 (Mild)	1324 (42.26)	8 (13.11)	377 (37.85)
Grade 2 (Moderate)	215 (6.86)	0 (0.00)	64 (6.43)
Grade 3 (Severe)	30 (0.96)	0 (0.00)	6 (0.60)
Grade 4 (Life Threatening)	0 (0.00)	0 (0.00)	0 (0.00)
Injection Site Redness			
Grade 1 (Mild)	75 (2.39)	0 (0.00)	15 (1.51)
Grade 2 (Moderate)	28 (0.89)	0 (0.00)	0 (0.00)
Grade 3 (Severe)	1 (0.03)	0 (0.00)	0 (0.00)
Grade 4 (Life Threatening)	0 (0.00)	0 (0.00)	0 (0.00)
Injection Site Swelling			
Grade 1 (Mild)	84 (2.68)	0 (0.00)	9 (0.90)
Grade 2 (Moderate)	29 (0.93)	0 (0.00)	1 (0.10)
Grade 3 (Severe)	1 (0.03)	0 (0.00)	0 (0.00)
Grade 4 (Life Threatening)	0 (0.00)	0 (0.00)	0 (0.00)
Solicited Local AEs after 2nd vaccine injection, n(%)			
Injection Site Pain			
Grade 1 (Mild)	954 (30.45)	8 (13.11)	181 (18.17)
Grade 2 (Moderate)	191 (6.10)	0 (0.00)	15 (1.51)
Grade 3 (Severe)	19 (0.61)	0 (0.00)	0 (0.00)
Grade 4 (Life Threatening)	0 (0.00)	0 (0.00)	0 (0.00)
Injection Site Redness			
Grade 1 (Mild)	55 (1.76)	0 (0.00)	6 (0.60)
Grade 2 (Moderate)	39 (1.24)	0 (0.00)	0 (0.00)
Grade 3 (Severe)	10 (0.32)	0 (0.00)	0 (0.00)
Grade 4 (Life Threatening)	0 (0.00)	0 (0.00)	0 (0.00)
Injection Site Swelling			
Grade 1 (Mild)	68 (2.17)	0 (0.00)	3 (0.30)
Grade 2 (Moderate)	30 (0.96)	0 (0.00)	0 (0.00)
Grade 3 (Severe)	3 (0.10)	0 (0.00)	0 (0.00)
Grade 4 (Life Threatening)	0 (0.00)	0 (0.00)	0 (0.00)

%: n / (No. of subject in Safety Set by group) * 100 The number of participants for safety set were displayed according to actual treatment group. One participant in GBP510_003 study was administered incorrect IP inconsistent (ChAdOx1-S) with randomisation assignment (GBP510 25ug+AS03).

Overall, injection site pain was the most frequently reported solicited local AE. Grade 1 (Mild) injection site pain occurred at a similar incidence rate in the GBP510 (1419 [45.29%]) and ChAdOx1-S (414 [41.57%]) arms. However, more reports of Grade 2 (Moderate) and Grade 3 (Severe) injection site pain events occurred in the GBP510 arm (317 [10.12%] and 47 [1.5%], respectively) compared to the ChAdOx1-S arm (66 [6.63%] and 6 [0.6%]). The difference in incidence rate of Grade 2 and Grade 3 injection site pain events between both arms was most apparent after the 2nd vaccination. In the placebo arm, only Grade 1 (Mild) injection site pain was reported, in 13 [21.31%] of subjects.

Injection site redness and injection site swelling were reported more frequently for every severity grade and after each injection in the GBP510 arm compared to the ChAdOx1-S arm. Grade 1, Grade 2, and Grade 3 injection site redness was reported at incidence rates of 107 [3.42%], 52 [1.66%] and 11 [0.35%], respectively, in the GBP510 arm, compared to 20 [2.01%], 0 [0%], and 0 [0%], respectively, in the ChAdOx1-S arm. Grade 1, Grade 2, and Grade 3 injection site swelling was reported at incidence rates of 132 [4.21%], 46 [1.47%], and 4 [0.13%], respectively, in the GBP510 arm, compared to 11 [1.10%], 1 [0.10%], and 0 [0%], respectively, in the ChAdOx1-S arm. No injection site redness or swelling were reported in the placebo arm.

Solicited Systemic Adverse Events

Solicited systemic AEs within 7 days following each vaccination by severity are presented in Table 22.

Table 22, Solicited Systemic Adverse Events, Following each Vaccination, by Severity (Safety Set)

		GBP510 25ug+AS03 N=3133 from 002 (N=104) and 003 (N=3029)	Placebo N=61 from 002	ChAdOx1-S N=996 from 003
Solicited Systemic AEs after any vaccine injection, n(%)				
Fever				
	Grade 1 (Mild)	272 (8.68)	1 (1.64)	88 (8.84)
	Grade 2 (Moderate)	163 (5.20)	0 (0.00)	45 (4.52)
	Grade 3 (Severe)	57 (1.82)	0 (0.00)	28 (2.81)
	Grade 4 (Life Threatening)	0 (0.00)	0 (0.00)	1 (0.10)
Nausea/Vomiting				
	Grade 1 (Mild)	198 (6.32)	5 (8.20)	63 (6.33)
	Grade 2 (Moderate)	29 (0.93)	1 (1.64)	14 (1.41)
	Grade 3 (Severe)	0 (0.00)	0 (0.00)	1 (0.10)
	Grade 4 (Life Threatening)	0 (0.00)	0 (0.00)	0 (0.00)
Diarrhea				
	Grade 1 (Mild)	153 (4.88)	4 (6.56)	70 (7.03)
	Grade 2 (Moderate)	28 (0.89)	1 (1.64)	10 (1.00)
	Grade 3 (Severe)	3 (0.10)	0 (0.00)	0 (0.00)
	Grade 4 (Life Threatening)	0 (0.00)	0 (0.00)	0 (0.00)
Headache				
	Grade 1 (Mild)	717 (22.89)	20 (32.79)	258 (25.90)
	Grade 2 (Moderate)	220 (7.02)	1 (1.64)	65 (6.53)
	Grade 3 (Severe)	27 (0.86)	0 (0.00)	8 (0.80)
	Grade 4 (Life Threatening)	0 (0.00)	0 (0.00)	0 (0.00)
Fatigue				
	Grade 1 (Mild)	661 (21.10)	24 (39.34)	205 (20.58)
	Grade 2 (Moderate)	291 (9.29)	6 (9.84)	101 (10.14)
	Grade 3 (Severe)	67 (2.14)	0 (0.00)	21 (2.11)
	Grade 4 (Life Threatening)	0 (0.00)	0 (0.00)	0 (0.00)
Myalgia				
	Grade 1 (Mild)	592 (18.90)	16 (26.23)	198 (19.88)
	Grade 2 (Moderate)	346 (11.04)	3 (4.92)	94 (9.44)
	Grade 3 (Severe)	68 (2.17)	0 (0.00)	15 (1.51)
	Grade 4 (Life Threatening)	0 (0.00)	0 (0.00)	0 (0.00)
Arthralgia				

	Grade 1 (Mild)	315 (10.05)	8 (13.11)	120 (12.05)
	Grade 2 (Moderate)	146 (4.66)	2 (3.28)	48 (4.82)
	Grade 3 (Severe)	28 (0.89)	0 (0.00)	8 (0.80)
	Grade 4 (Life Threatening)	0 (0.00)	0 (0.00)	0 (0.00)
Chills				
	Grade 1 (Mild)	490 (15.64)	6 (9.84)	155 (15.56)
	Grade 2 (Moderate)	202 (6.45)	3 (4.92)	70 (7.03)
	Grade 3 (Severe)	50 (1.60)	1 (1.64)	21 (2.11)
	Grade 4 (Life Threatening)	0 (0.00)	0 (0.00)	0 (0.00)
Solicited Systemic AEs after 1st vaccine injection, n(%)				
Fever				
	Grade 1 (Mild)	116 (3.70)	1 (1.64)	85 (8.53)
	Grade 2 (Moderate)	60 (1.92)	0 (0.00)	38 (3.82)
	Grade 3 (Severe)	21 (0.67)	0 (0.00)	27 (2.71)
	Grade 4 (Life Threatening)	0 (0.00)	0 (0.00)	1 (0.10)
Nausea/Vomiting				
	Grade 1 (Mild)	112 (3.57)	3 (4.92)	51 (5.12)
	Grade 2 (Moderate)	15 (0.48)	0 (0.00)	12 (1.20)
	Grade 3 (Severe)	0 (0.00)	0 (0.00)	0 (0.00)
	Grade 4 (Life Threatening)	0 (0.00)	0 (0.00)	0 (0.00)
Diarrhoea				
	Grade 1 (Mild)	100 (3.19)	4 (6.56)	50 (5.02)
	Grade 2 (Moderate)	14 (0.45)	0 (0.00)	8 (0.80)
	Grade 3 (Severe)	2 (0.06)	0 (0.00)	0 (0.00)
	Grade 4 (Life Threatening)	0 (0.00)	0 (0.00)	0 (0.00)
Headache				
	Grade 1 (Mild)	512 (16.34)	12 (19.67)	221 (22.19)
	Grade 2 (Moderate)	94 (3.00)	0 (0.00)	60 (6.02)
	Grade 3 (Severe)	10 (0.32)	0 (0.00)	7 (0.70)
	Grade 4 (Life Threatening)	0 (0.00)	0 (0.00)	0 (0.00)
Fatigue				
	Grade 1 (Mild)	520 (16.60)	22 (36.07)	189 (18.98)
	Grade 2 (Moderate)	167 (5.33)	3 (4.92)	93 (9.34)
	Grade 3 (Severe)	22 (0.70)	0 (0.00)	21 (2.11)
	Grade 4 (Life Threatening)	0 (0.00)	0 (0.00)	0 (0.00)
Myalgia				
	Grade 1 (Mild)	513 (16.37)	12 (19.67)	179 (17.97)
	Grade 2 (Moderate)	234 (7.47)	1 (1.64)	90 (9.04)
	Grade 3 (Severe)	39 (1.24)	0 (0.00)	14 (1.41)
	Grade 4 (Life Threatening)	0 (0.00)	0 (0.00)	0 (0.00)
Arthralgia				
	Grade 1 (Mild)	226 (7.21)	3 (4.92)	107 (10.74)
	Grade 2 (Moderate)	67 (2.14)	0 (0.00)	41 (4.12)
	Grade 3 (Severe)	9 (0.29)	0 (0.00)	8 (0.80)
	Grade 4 (Life Threatening)	0 (0.00)	0 (0.00)	0 (0.00)
Chills				
	Grade 1 (Mild)	286 (9.13)	1 (1.64)	142 (14.26)
	Grade 2 (Moderate)	53 (1.69)	0 (0.00)	66 (6.63)
	Grade 3 (Severe)	12 (0.38)	0 (0.00)	20 (2.01)
	Grade 4 (Life Threatening)	0 (0.00)	0 (0.00)	0 (0.00)
Solicited Systemic AEs after 2nd vaccine injection, n(%)				
Fever				
	Grade 1 (Mild)	203 (6.48)	0 (0.00)	8 (0.80)
	Grade 2 (Moderate)	112 (3.57)	0 (0.00)	7 (0.70)
	Grade 3 (Severe)	40 (1.28)	0 (0.00)	1 (0.10)
	Grade 4 (Life Threatening)	0 (0.00)	0 (0.00)	0 (0.00)
Nausea/Vomiting				
	Grade 1 (Mild)	120 (3.83)	2 (3.28)	24 (2.41)
	Grade 2 (Moderate)	17 (0.54)	1 (1.64)	2 (0.20)
	Grade 3 (Severe)	0 (0.00)	0 (0.00)	1 (0.10)
	Grade 4 (Life Threatening)	0 (0.00)	0 (0.00)	0 (0.00)

Diarrhoea				
	Grade 1 (Mild)	77 (2.46)	1 (1.64)	28 (2.81)
	Grade 2 (Moderate)	14 (0.45)	1 (1.64)	3 (0.30)
	Grade 3 (Severe)	1 (0.03)	0 (0.00)	0 (0.00)
	Grade 4 (Life Threatening)	0 (0.00)	0 (0.00)	0 (0.00)
Headache				
	Grade 1 (Mild)	467 (14.91)	12 (19.67)	102 (10.24)
	Grade 2 (Moderate)	166 (5.30)	1 (1.64)	17 (1.71)
	Grade 3 (Severe)	19 (0.61)	0 (0.00)	2 (0.20)
	Grade 4 (Life Threatening)	0 (0.00)	0 (0.00)	0 (0.00)
Fatigue				
	Grade 1 (Mild)	456 (14.55)	19 (31.15)	107 (10.74)
	Grade 2 (Moderate)	219 (6.99)	5 (8.20)	25 (2.51)
	Grade 3 (Severe)	49 (1.56)	0 (0.00)	1 (0.10)
	Grade 4 (Life Threatening)	0 (0.00)	0 (0.00)	0 (0.00)
Myalgia				
	Grade 1 (Mild)	387 (12.35)	8 (13.11)	89 (8.94)
	Grade 2 (Moderate)	225 (7.18)	3 (4.92)	21 (2.11)
	Grade 3 (Severe)	43 (1.37)	0 (0.00)	1 (0.10)
	Grade 4 (Life Threatening)	0 (0.00)	0 (0.00)	0 (0.00)
Arthralgia				
	Grade 1 (Mild)	183 (5.84)	6 (9.84)	39 (3.92)
	Grade 2 (Moderate)	104 (3.32)	2 (3.28)	11 (1.10)
	Grade 3 (Severe)	21 (0.67)	0 (0.00)	0 (0.00)
	Grade 4 (Life Threatening)	0 (0.00)	0 (0.00)	0 (0.00)
Chills				
	Grade 1 (Mild)	335 (10.69)	6 (9.84)	42 (4.22)
	Grade 2 (Moderate)	164 (5.23)	3 (4.92)	5 (0.50)
	Grade 3 (Severe)	38 (1.21)	1 (1.64)	1 (0.10)
	Grade 4 (Life Threatening)	0 (0.00)	0 (0.00)	0 (0.00)

%: n / (No. of subject in Safety Set by group) * 100 The number of participants for safety set were displayed according to actual treatment group. One participant in GBP510_003 study was administered incorrect IP inconsistent (ChAdOx1-S) with randomisation assignment (GBP510 25ug+AS03).

The most commonly reported systemic AEs after any vaccination were fever (GBP510: 16%, Placebo: 2%, ChAdOx: 16%), nausea/vomiting (GBP510: 7%, Placebo:10%, ChAdOx: 8%), diarrhoea (GBP510: 6%, Placebo:8%, ChAdOx: 8%), headache (GBP510: 31%, Placebo:34%, ChAdOx: 33%), fatigue (GBP510: 33%, Placebo:49%, ChAdOx: 33%), myalgia (GBP510: 32%, Placebo:31%, ChAdOx: 31%), arthralgia (GBP510: 6%, Placebo:3%, ChAdOx: 6%), and chills (GBP510: 8%, Placebo:7%, ChAdOx: 9%).

When considering the overall incidence rate (after any dose), systemic AEs occurred at similar incidence rates for each severity level when comparing the GBP150 and ChAdOx1-S arms. However, when considering the injections separately: after the 1st injection, systemic AEs tended to be slightly lower in the GBP150 arm than in the ChAdOx1-S arm at all severity levels, while the opposite was seen after the 2nd injection.

Unsolicited AEs

Overall, the incidence rate of unsolicited AEs was similar between treatment arms (421 [13.44%] for the GBP510 arm, 145 [14.56%] for the ChAdOx1-S arm, and 10 [16.39%] for the placebo arm), as was the incidence rate of MAAEs (150 [4.79%], 46 [4.62%], and 4 [6.56%], respectively).

Infections and infestations were the most frequently reported, with incidence rates of 182 [5.81%] in the GBP510 arm, and 59 [5.92%] in the ChAdOx1-S arm. For both the GBP510 and ChAdOx1-S arms, most of these events were COVID-19 or suspected COVID-19. All other unsolicited AEs occurred at similar incidence rates between treatment arms; and this was similar when considering each injection separately.

Table 23. Unsolicited AEs by PT and SOC after any dose (Showing PTs where >1 participant reported an AE in any treatment arm; Safety Set)

System Organ Class Preferred Term	GBP510 25ug+AS03 N=3133 from 002 (N=104) and 003 (N=3029) *n persons, (%), [n events]*	Placebo N=61 from 002 *n persons, (%), [n events]*	ChAdOx1-S N=996 from 003 *n persons, (%), [n events]*
Unsolicited AEs after any vaccine injection	421 (13.44) [671]	10 (16.39) [16]	145 (14.56) [213]
Infections and infestations	182 (5.81) [192]	0 (0.00) [0]	59 (5.92) [60]
COVID-19	62 (1.98) [62]	0 (0.00) [0]	33 (3.31) [33]
Suspected COVID-19	48 (1.53) [48]	0 (0.00) [0]	11 (1.10) [11]
Upper respiratory tract infection	19 (0.61) [19]	0 (0.00) [0]	3 (0.30) [3]
Nasopharyngitis	11 (0.35) [12]	0 (0.00) [0]	4 (0.40) [4]
Rhinitis	7 (0.22) [8]	0 (0.00) [0]	2 (0.20) [2]
Systemic viral infection	7 (0.22) [7]	0 (0.00) [0]	0 (0.00) [0]
Tonsillitis	2 (0.06) [2]	0 (0.00) [0]	3 (0.30) [3]
Conjunctivitis	3 (0.10) [3]	0 (0.00) [0]	0 (0.00) [0]
Herpes virus infection	2 (0.06) [2]	0 (0.00) [0]	1 (0.10) [1]
Viral infection	3 (0.10) [3]	0 (0.00) [0]	0 (0.00) [0]
Influenza	1 (0.03) [2]	0 (0.00) [0]	1 (0.10) [1]
Furuncle	2 (0.06) [2]	0 (0.00) [0]	0 (0.00) [0]
Gastroenteritis	2 (0.06) [2]	0 (0.00) [0]	0 (0.00) [0]
Hordeolum	2 (0.06) [2]	0 (0.00) [0]	0 (0.00) [0]
Urinary tract infection	2 (0.06) [2]	0 (0.00) [0]	0 (0.00) [0]
Vaginal infection	2 (0.06) [2]	0 (0.00) [0]	0 (0.00) [0]
Nervous system disorders	59 (1.88) [72]	1 (1.64) [2]	25 (2.51) [29]
Headache	21 (0.67) [26]	0 (0.00) [0]	8 (0.80) [8]
Dizziness	18 (0.57) [20]	0 (0.00) [0]	11 (1.10) [11]
Hypoaesthesia	3 (0.10) [4]	0 (0.00) [0]	3 (0.30) [3]
Paraesthesia	5 (0.16) [6]	0 (0.00) [0]	1 (0.10) [1]
Somnolence	4 (0.13) [4]	0 (0.00) [0]	2 (0.20) [3]
Paralysis	2 (0.06) [2]	0 (0.00) [0]	0 (0.00) [0]
Syncope	2 (0.06) [2]	0 (0.00) [0]	0 (0.00) [0]
Musculoskeletal and connective tissue disorders	61 (1.95) [78]	2 (3.28) [2]	18 (1.81) [21]
Back pain	10 (0.32) [10]	1 (1.64) [1]	5 (0.50) [5]
Arthralgia	12 (0.38) [15]	0 (0.00) [0]	3 (0.30) [4]
Myalgia	13 (0.41) [15]	0 (0.00) [0]	2 (0.20) [2]
Pain in extremity	9 (0.29) [11]	0 (0.00) [0]	0 (0.00) [0]
Groin pain	4 (0.13) [4]	0 (0.00) [0]	0 (0.00) [0]
Musculoskeletal chest pain	2 (0.06) [2]	0 (0.00) [0]	1 (0.10) [1]
Musculoskeletal stiffness	2 (0.06) [3]	0 (0.00) [0]	0 (0.00) [0]
Flank pain	2 (0.06) [2]	0 (0.00) [0]	0 (0.00) [0]
Limb discomfort	2 (0.06) [2]	0 (0.00) [0]	0 (0.00) [0]
General disorders and administration site conditions	59 (1.88) [83]	0 (0.00) [0]	19 (1.91) [21]
Pain	13 (0.41) [14]	0 (0.00) [0]	1 (0.10) [1]
Injection site pruritus	11 (0.35) [14]	0 (0.00) [0]	2 (0.20) [2]
Chest pain	9 (0.29) [10]	0 (0.00) [0]	4 (0.40) [5]
Chest discomfort	6 (0.19) [7]	0 (0.00) [0]	2 (0.20) [2]
Pyrexia	4 (0.13) [4]	0 (0.00) [0]	3 (0.30) [3]
Fatigue	4 (0.13) [4]	0 (0.00) [0]	1 (0.10) [1]
Injection site warmth	4 (0.13) [5]	0 (0.00) [0]	0 (0.00) [0]
Chills	4 (0.13) [4]	0 (0.00) [0]	0 (0.00) [0]
Asthenia	2 (0.06) [2]	0 (0.00) [0]	1 (0.10) [1]
Feeling hot	3 (0.10) [3]	0 (0.00) [0]	0 (0.00) [0]
Injection site bruising	3 (0.10) [3]	0 (0.00) [0]	0 (0.00) [0]
Respiratory, thoracic and mediastinal disorders	48 (1.53) [61]	1 (1.64) [3]	19 (1.91) [25]
Cough	17 (0.54) [18]	0 (0.00) [0]	6 (0.60) [6]
Rhinorrhoea	15 (0.48) [15]	0 (0.00) [0]	7 (0.70) [7]
Oropharyngeal pain	14 (0.45) [15]	0 (0.00) [0]	5 (0.50) [5]
Rhinitis allergic	4 (0.13) [4]	1 (1.64) [3]	0 (0.00) [0]
Allergic cough	2 (0.06) [2]	0 (0.00) [0]	1 (0.10) [1]
Gastrointestinal disorders	42 (1.34) [52]	0 (0.00) [0]	17 (1.71) [19]

Toothache	8 (0.26) [9]	0 (0.00) [0]	1 (0.10) [1]
Dyspepsia	6 (0.19) [6]	0 (0.00) [0]	2 (0.20) [2]
Abdominal pain upper	2 (0.06) [2]	0 (0.00) [0]	5 (0.50) [5]
Gastroesophageal reflux disease	4 (0.13) [4]	0 (0.00) [0]	3 (0.30) [3]
Diarrhoea	6 (0.19) [7]	0 (0.00) [0]	0 (0.00) [0]
Abdominal pain	4 (0.13) [4]	0 (0.00) [0]	1 (0.10) [1]
Stomatitis	2 (0.06) [3]	0 (0.00) [0]	2 (0.20) [2]
Nausea	3 (0.10) [4]	0 (0.00) [0]	0 (0.00) [0]
Mouth ulceration	2 (0.06) [2]	0 (0.00) [0]	1 (0.10) [1]
Haemorrhoids	2 (0.06) [2]	0 (0.00) [0]	0 (0.00) [0]
Skin and subcutaneous tissue disorders	24 (0.77) [26]	1 (1.64) [1]	6 (0.60) [7]
Rash	7 (0.22) [7]	0 (0.00) [0]	0 (0.00) [0]
Urticaria	5 (0.16) [6]	0 (0.00) [0]	1 (0.10) [1]
Pruritus	5 (0.16) [5]	0 (0.00) [0]	1 (0.10) [1]
Hyperhidrosis	2 (0.06) [2]	0 (0.00) [0]	2 (0.20) [2]
Dermatitis	2 (0.06) [2]	0 (0.00) [0]	0 (0.00) [0]
Injury, poisoning and procedural complications	18 (0.57) [20]	1 (1.64) [1]	6 (0.60) [6]
Skin laceration	5 (0.16) [5]	0 (0.00) [0]	0 (0.00) [0]
Arthropod sting	3 (0.10) [3]	0 (0.00) [0]	0 (0.00) [0]
Joint injury	2 (0.06) [2]	0 (0.00) [0]	1 (0.10) [1]
Hand fracture	2 (0.06) [2]	0 (0.00) [0]	0 (0.00) [0]
Limb injury	0 (0.00) [0]	0 (0.00) [0]	2 (0.20) [2]
Reproductive system and breast disorders	13 (0.41) [19]	1 (1.64) [1]	6 (0.60) [6]
Dysmenorrhoea	6 (0.19) [7]	1 (1.64) [1]	2 (0.20) [2]
Vaginal haemorrhage	1 (0.03) [1]	0 (0.00) [0]	2 (0.20) [2]
Premenstrual syndrome	2 (0.06) [2]	0 (0.00) [0]	0 (0.00) [0]
Metrorrhagia	1 (0.03) [2]	0 (0.00) [0]	0 (0.00) [0]
Ear and labyrinth disorders	10 (0.32) [10]	0 (0.00) [0]	2 (0.20) [2]
Ear discomfort	2 (0.06) [2]	0 (0.00) [0]	1 (0.10) [1]
Ear pain	3 (0.10) [3]	0 (0.00) [0]	0 (0.00) [0]
Vertigo	2 (0.06) [2]	0 (0.00) [0]	0 (0.00) [0]
Vascular disorders	8 (0.26) [8]	0 (0.00) [0]	3 (0.30) [3]
Hypertension	6 (0.19) [6]	0 (0.00) [0]	3 (0.30) [3]
Cardiac disorders	6 (0.19) [7]	0 (0.00) [0]	4 (0.40) [4]
Palpitations	5 (0.16) [5]	0 (0.00) [0]	3 (0.30) [3]
Metabolism and nutrition disorders	8 (0.26) [10]	1 (1.64) [1]	0 (0.00) [0]
Decreased appetite	5 (0.16) [6]	0 (0.00) [0]	0 (0.00) [0]
Obesity	2 (0.06) [2]	0 (0.00) [0]	0 (0.00) [0]
Investigations	4 (0.13) [4]	4 (6.56) [5]	0 (0.00) [0]
Blood triglycerides increased	2 (0.06) [2]	1 (1.64) [1]	0 (0.00) [0]
Blood and lymphatic system disorders	4 (0.13) [4]	0 (0.00) [0]	0 (0.00) [0]
Lymphadenopathy	2 (0.06) [2]	0 (0.00) [0]	0 (0.00) [0]
Surgical and medical procedures	3 (0.10) [3]	0 (0.00) [0]	1 (0.10) [1]
Tooth extraction	2 (0.06) [2]	0 (0.00) [0]	0 (0.00) [0]

%: n / (No. of subject in Safety Set by group) * 100 The number of participants for safety set were displayed according to actual treatment group. One participant in GBP510_003 study was administered incorrect IP inconsistent (ChAdOx1-S) with randomisation assignment (GBP510 25ug+AS03).

Related Unsolicited AEs

Overall, related unsolicited AEs occurred at a similar frequency after each injection, for all treatment arms (111 [3.54%] in the GBP510 arm, 41 [4.12%%] in the ChAdOx1-S arm, and 2 [3.28%] in the placebo arm). General disorders and administration site conditions were the most frequently reported, with incidence rates of 40 [1.28%] for the GBP510 arm and 10 [1.00%] in the ChAdOx1-S arm. No such events were reported for the placebo arm (0 [0%]). All other unsolicited AEs occurred at similar incidence rates between treatments, and this was similar when considering each injection separately.

Table 24. Related unsolicited AEs by PT and SOC (reported by >1 participant in any treatment arm, Safety Set)

System Organ Class Preferred Term	GBP510 25ug+AS03 N=3133 from 002 (N=104) and 003 (N=3029) *n persons, (%), [n events]*	Placebo N=61 from 002 *n persons, (%), [n events]*	ChAdOx1-S N=996 from 003 *n persons, (%), [n events]*
Related Unsolicited AEs after any vaccine injection	111 (3.54) [173]	2 (3.28) [2]	41 (4.12) [59]
General disorders and administration site conditions	40 (1.28) [52]	0 (0.00) [0]	10 (1.00) [11]
Injection site pruritus	11 (0.35) [14]	0 (0.00) [0]	2 (0.20) [2]
Pain	8 (0.26) [9]	0 (0.00) [0]	1 (0.10) [1]
Chest pain	5 (0.16) [5]	0 (0.00) [0]	1 (0.10) [2]
Injection site warmth	4 (0.13) [5]	0 (0.00) [0]	0 (0.00) [0]
Chest discomfort	2 (0.06) [2]	0 (0.00) [0]	2 (0.20) [2]
Injection site pain	1 (0.03) [1]	0 (0.00) [0]	2 (0.20) [2]
Asthenia	2 (0.06) [2]	0 (0.00) [0]	0 (0.00) [0]
Injection site bruising	2 (0.06) [2]	0 (0.00) [0]	0 (0.00) [0]
Nervous system disorders	26 (0.83) [31]	0 (0.00) [0]	14 (1.41) [16]
Dizziness	10 (0.32) [12]	0 (0.00) [0]	7 (0.70) [7]
Hypoaesthesia	3 (0.10) [4]	0 (0.00) [0]	3 (0.30) [3]
Paraesthesia	4 (0.13) [5]	0 (0.00) [0]	0 (0.00) [0]
Somnolence	1 (0.03) [1]	0 (0.00) [0]	2 (0.20) [3]
Headache	2 (0.06) [2]	0 (0.00) [0]	1 (0.10) [1]
Musculoskeletal and connective tissue disorders	23 (0.73) [27]	0 (0.00) [0]	8 (0.80) [10]
Back pain	3 (0.10) [3]	0 (0.00) [0]	3 (0.30) [3]
Arthralgia	3 (0.10) [3]	0 (0.00) [0]	2 (0.20) [3]
Pain in extremity	4 (0.13) [5]	0 (0.00) [0]	0 (0.00) [0]
Groin pain	2 (0.06) [2]	0 (0.00) [0]	0 (0.00) [0]
Limb discomfort	2 (0.06) [2]	0 (0.00) [0]	0 (0.00) [0]
Gastrointestinal disorders	10 (0.32) [12]	0 (0.00) [0]	7 (0.70) [8]
Abdominal pain	3 (0.10) [3]	0 (0.00) [0]	1 (0.10) [1]
Stomatitis	1 (0.03) [2]	0 (0.00) [0]	2 (0.20) [2]
Dyspepsia	2 (0.06) [2]	0 (0.00) [0]	1 (0.10) [1]
Abdominal pain upper	0 (0.00) [0]	0 (0.00) [0]	2 (0.20) [2]
Nausea	2 (0.06) [2]	0 (0.00) [0]	0 (0.00) [0]
Skin and subcutaneous tissue disorders	12 (0.38) [13]	1 (1.64) [1]	3 (0.30) [4]
Rash	4 (0.13) [4]	0 (0.00) [0]	0 (0.00) [0]
Hyperhidrosis	2 (0.06) [2]	0 (0.00) [0]	1 (0.10) [1]
Pruritus	3 (0.10) [3]	0 (0.00) [0]	0 (0.00) [0]
Urticaria	2 (0.06) [2]	0 (0.00) [0]	1 (0.10) [1]
Respiratory, thoracic and mediastinal disorders	8 (0.26) [10]	0 (0.00) [0]	3 (0.30) [3]
Cough	4 (0.13) [4]	0 (0.00) [0]	1 (0.10) [1]
Oropharyngeal pain	4 (0.13) [4]	0 (0.00) [0]	1 (0.10) [1]
Rhinorrhoea	2 (0.06) [2]	0 (0.00) [0]	0 (0.00) [0]
Cardiac disorders	4 (0.13) [4]	0 (0.00) [0]	2 (0.20) [2]
Palpitations	4 (0.13) [4]	0 (0.00) [0]	2 (0.20) [2]
Infections and infestations	4 (0.13) [4]	0 (0.00) [0]	2 (0.20) [2]
Nasopharyngitis	1 (0.03) [1]	0 (0.00) [0]	1 (0.10) [1]
Upper respiratory tract infection	2 (0.06) [2]	0 (0.00) [0]	0 (0.00) [0]

Coding Dictionary: MedDRA version 23.1 (GBP510_002) & MedDRA version 24.0 (GBP510_003)
Solicited AEs are summarised by reported term %: n / (No. of subject in Safety Set by group) × 100
The number of participants for safety set were displayed according to actual treatment group. One participant in GBP510_003 study was administered incorrect IP inconsistent (ChAdOx1-S) with randomisation assignment (GBP510 25ug+AS03). The relationship of the case in (ChAdOx1-S) group is 'Not related'.

3.3.7.3. Serious adverse events, deaths, and other significant events

Deaths

There were no deaths in GBP510_002. There were two deaths reported in GBP510_003, one in the GBP510 treatment arm and one in the control treatment arm.

One death due to cardio-respiratory failure was reported in the ChAdOx1-S treatment arm in a participant with uncontrollable hypertension. This was assessed to be serious, unexpected and not related to the study drug.

After a 3-month follow up, one death due to brain neoplasm was reported in the GBP510 treatment arm. This case was assessed as not related to the study drug.

Other SAEs

In Study GBP510_002, there were 3 SAEs reported in 3 subjects: haemorrhoids in 1 subject in the GBP510 25 µg adjuvanted with AS03 group, breast cancer and road traffic accident in 1 subject each in the GBP510 25 µg group. None were considered related to study treatment. During the 6-month follow-up period in GBP510_002, 5 additional SAEs in 4 subjects in the GBP510 25ug with AS03 group (Nephrolithiasis and Ureterolithiasis; Abortion spontaneous; COVID-19 (hospitalisation), Traffic accident), 1 SAE in 1 subject in the GBP510 25ug group (Ovarian cancer) and 1 SAE in 1 subject in the GBP510 10ug group (Appendicitis) have been reported.

In Study GBP510_003, there were 22 participants reporting a total of 24 SAEs. Of these, 9 concerned serious COVID-19 reports. Further, 15 SAEs were reported in 13 participants, 10 (n=10) in the GPB510 group and 5 (n=3) in the ChAdOx-1 group.

SAEs reported in the GBP510 group were: appendicitis, hand fracture, pneumonia, rotator cuff syndrome, anal abscess, skin laceration, Schizophrenia', 'Glomerulonephritis rapidly progressive', 'Acute myocardial infarction', 'Gastroesophageal reflux disease'.

Of these, 'Glomerulonephritis rapidly progressive' was considered related by the investigator and Applicant. This event occurred in a young male with no relevant family history (renal conditions, autoimmune disease, allergic reaction) or medical history (renal diseases, sore throat, skin infection, or any bacterial or viral infection). The participant developed symptoms consisting of facial edema and abdominal pain 3 days after injection of GBP510. At day 14 after the injection, he was started on cefuroxime and cetirizine for suspected infection. The participant was admitted to hospital on an unknown date. The differential diagnosis was UTI, hypersensitivity reaction or glomerulonephritis. A renal biopsy was performed, and he was started on corticosteroids. Edema persisted, and the urine was discoloured. One month after the injection of GBP510, the diagnosis of RPGN and nephrotic syndrome was established. From week 5-6 on he improved with decreases in proteinuria. At month 4, corticosteroids were temporarily increased because of an increase in proteinuria. This SAE was assessed as 'Related' to the IP (GBP510) by the investigator, SK bioscience Co., Ltd. and International Vaccine Institute because not only the time interval between the IP (GBP510) administration and the event makes a temporal relationship of the IP (GBP510) to the event as reasonable but also since the causal relationship with the IP (GBP510) could not be fully excluded.

AESIs

In the pooled data set, there were a total of 3 AESIs, 2 (0.06%) in the GBP510 arm (acute kidney injury, glomerulonephritis rapidly progressive) and 1 (0.10%) in the ChAdOx1-S arm (pancreatitis acute) coming from the study GBP510_003.

MAAEs

Medically attended adverse events occurring 28 days after any vaccination were reported in 156 (4.98%) subjects in the GBP510 arm, 50 (5.02%) subjects in the ChAdOx1-S arm, and 4 (6.56%) subjects in the placebo group (Table 24)**.**

MAAEs have been discussed per study.

In GBP510_003, cumulatively for up to 3 months post-vaccination, MAAEs have occurred in 227 (7.49%; 279 cases) participants in the treatment group and 84 (8.43%; 122 cases) participants in the control group.

The most reported MAAEs by SOC were infections and infestation (155 participants (5.12%) in the GBP510 group, 54 (5.45%) in the ChAdOx1-S group), musculoskeletal and connective tissue disorders (19 participants (0.63%) in the GBP510 group, 11 (1.10%) in the ChAdOx1-S group) and gastrointestinal disorders (10 participants (0.33%) in the GBP510 group, 10 (1.00%) in the ChAdOx1-S group). The most reported MAAEs by PT were COVID-19 (2.34%; 94 participants; 94 cases) and suspected COVID-19 (1.69%; 68 participants; 68 cases).

In GBP510_002, cumulatively up to 6 months post-vaccination, the MAAEs have been reported in 12 (11.9%) subjects in the in the GBP510 10 µg with AS03 group, 2 (20.0%) subjects in the GBP510 10 µg group, 16 (15.4%) subjects in the GBP510 25 µg with AS03 group, 9 (17.7%) subjects in GBP510 25 µg group, and 7 (11.5%) subjects in the placebo group. The most reported MAAEs by SOC were infections and infestation (7 participants of whom 3 (2.97%) in the GBP510 25 µg with AS03 group) and skin and subcutaneous tissue disorders (5 participants of whom 3 (2.97%) in the GBP510 25 µg with AS03 group).

3.3.7.4. Laboratory findings

Haematology and clinical chemistry were assessed in phase 2 study GBP510_002. Summaries of categories relative to the clinical significance of all results of clinical laboratory tests (Haematology/Blood biochemistry/Urinalysis test) categorised by 'Normal/Not Clinically Significant (NCS)', 'Clinically Significant (CS)' were provided with shifts from screening to post-screening visits (Visit 3: Only for sentinel group, Visit 7).

Haematology

At Visit 3 and Visit 7, all but 2 subjects had no clinically significant changes in haematology parameters. At Visit 7, 1 subject in the GBP510 10 µg adjuvanted with AS03 group and 1 subject in the placebo group had a shift from normal to a clinically significant change in white blood cells and eosinophils, respectively. All subjects who had a shift from normal to a significant change had recovered or stabilised.

Clinical chemistry

In Study GBP510_002, at Visit 3 and Visit 7, all but 9 subjects had no clinically significant changes in clinical chemistry parameters. At Visit 7, shifts from normal to a clinically significant change were reported.

- Alanine aminotransferase (ALT; GPT) in 1 (1.0%) subject in the GBP510 10 µg adjuvanted with AS03 group and 1 (1.7%) subject in the placebo group
- Aspartate aminotransferase (AST; GOT) in 1 (1.7%) subject in the placebo group
- Uric acid in 1 (1.7%) subject in the placebo group
- Total cholesterol in 1 (2.0%) subject in the GBP510 25 µg group
- Triglyceride in 3 (2.9%) subjects in the GBP510 25 µg adjuvanted with AS03 group and 1 (1.7%) subject in the placebo group. Triglyceride rises were resolved in all the subjects.

Urinalysis

Of the 16 sentinel subjects in Study GBP510_002, there was no shift in the urinalysis tests across treatment groups.

Electrocardiogram

In Study GBP510_003, electrocardiogram (ECG) measurements were not obtained. In Study GBP510_002, a 12-lead ECG was performed in 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. 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. There was no subject with clinically significant results in 12-lead ECG during this study.

3.3.7.5. In vitro biomarker test for patient selection for safety

Not applicable.

3.3.7.6. Safety in special populations

Subgroup analyses for age (19-64 years, ⩾ 65 years) and sex (male, female) were conducted on the Safety Sets for each study separately. Further, the safety by ethnicity and/or region is of interest due to the extrapolation of data to the European setting.

In Study GBP510_002, no notable findings or trends in the AE profile observed across all treatment groups for the different subgroups of age (19-64 years) and sex (male, female); the age subgroup of ⩾ 65 years could not be compared due to the limited sample size. No trends were noted for overall summary of AEs.

In Study GBP510_003, no notable findings or trends in the AE profile were observed across treatment groups by gender (male, female) and age (18-64 and ⩾ 65 years), although the sample size for the age group ⩾ 65 years was limited.

By age:

In **GBP510_002**, of 328 participants in the ITT Set, '19~64 years' participants were 89.33% (293/328 participants) and '65~85 years' participants were 10.67% (35/328 participants) with only 12 participants aged 65 to 85 who received GBP510 25 ug with AS03. The age subgroup of ⩾ 65 years could not be compared due to the limited sample size.

Of total 4,025 participants in the Safety Set in **GBP510_003**, 2,871 participants in GBP510 group (94.78%) and 941 participants in ChAdOx1-S (94.48%) were aged between 18 to 64 years old (younger aged participants). Elderly participants (⩾ 65 years) in each group were 158 participants in GBP510 group (5.22%) and 55 participants in ChAdOx1-S group (5.52%).

In solicited local AEs, the proportion of participants who reported AEs after any vaccination in each age strata was 56.7% in GBP510 group and 49.4% in ChAdOx1-S group for younger aged participants and 56.3% in GBP510 group and 45.5% in ChAdOx1-S group for elderly participants.

In solicited systemic AEs, the proportion of participants who reported AEs after any vaccination in each age strata was 51.4% in GBP510 group and 53.7% in ChAdOx1-S group for younger aged participants and 47.5% in GBP510 group and 50.9% in ChAdOx1-S group for elderly participants. The most frequently reported AEs were, 'Headache', 'Myalgia', and 'Fatigue' across all age groups after any vaccination.

The proportion of participants who reported SAE, AESI, MAAE, and MAADR after any vaccination in younger aged participants was 0.5%, 0.1%, 5% and 0.6% in GBP510 group and 0.6%, 0.1%, 5% and 1.1% in ChAdOx1-S group, respectively.

By sex:

In **GBP510_002**: Of 328 participants in the ITT Set, 'Male' participants were 45.12% (148/328 participants) and 'Female' participants were 54.88% (180/328 participants). In the GBP510 25 ug with AS03 group, 43.3% (45/104 participants) was male. In Study GBP510_002, no notable findings or trends in the AE profile observed across all treatment groups for the different subgroups of gender (male, female).

In **GBP510_003**, 59.7 % (1,814/3,039 participants) of GBP510 group and 57.4 % (572/997 participants) of ChAdOx1-S group were male participants.

In Study GBP510_003, no notable findings or trends in the AE profile were observed across treatment groups by gender (male, female).

By ethnicity:

GBP510_002 only included centres in South Korea. All the participants were 'Korean' in all treatment groups.

For **GBP510_003**, when AEs were analysed by each ethnicity, the proportion of Korean participants that reported solicited local/systemic AEs were noticeably higher (96.94%/93.58% in GBP510 group and 85.12%/ 92.86% in ChAdOx1-S group) than in Southeast Asian participants (49.90%/43.95% in GBP510 group and 39.68%/43.76% in ChAdOx1-S group), who constituted the majority of the participants enrolled in the 003 study. In the GBP510_002 study, which only involved Korean participants, the proportion of participants who reported solicited local and systemic AE were 92.31% and 85.58% after any vaccination, respectively. This high incidence rate of solicited AEs observed in 002 study were similar to the trend of solicited AEs observed in the Korean participants in the 003 study, which could explain the lower reactogenicity observed in the 003 study as compared to the 002 study. Incidence of SAEs was similar across race subgroups.

Use in Pregnancy and Lactation

In all three clinical studies, women were excluded from the study if they presented with a positive serum or urine pregnancy test at enrolment and a positive pregnancy test prior to each vaccination. In total, 7 pregnancies have occurred in both trials. Six pregnancies have no outcome yet and are being monitored. One pregnancy resulted in a spontaneous abortion. The subject received treatment with GBP510 25 µg adjuvanted with AS03, with the second dose received in 6/2021. The pregnancy was confirmed 9/2021 when the subject was at 5 weeks of gestation. The spontaneous abortion was reported as an SAE and deemed not related to the study vaccine by the Study Investigator.

3.3.7.7. Immunological events

Not applicable

3.3.7.8. Safety related to drug-drug interactions and other interactions

Not applicable

3.3.7.9. Discontinuation due to adverse events

In Study **GBP510_002**, of the 329 subjects in the Safety Set, two subjects experienced a treatment-emergent adverse event (TEAE) that led to treatment discontinuation: vision blurred, myalgia, tension headache in one subject in the GBP510 25 µg group which was considered related to the vaccine, and breast cancer in one subject in the GBP510 25 µg adjuvanted with AS03 group, which was not related to the vaccine.

In total, 5 participants (3 participants in GBP510 group and 2 participants in ChAdOx1-S group) in **GBP510_003** were withdrawn due to AEs; these reported 11 AEs. Of these, 6 AEs which occurred in one participant, were reported as 'related to study vaccine' and included 'urticaria rash '(Grade 1), 'injection site pain' (Grade 3), 'headache' (Grade 1), 'fatigue' (Grade 2), 'myalgia'(Grade 2), and 'arthralgia' (Grade 1), which lasted from 30-NOV-2021 to 04-DEC-2021. All AEs resolved.

3.3.7.10. Post marketing experience

Not applicable

3.3.8. Discussion on clinical safety

GBP510 is a RBD nanoparticle, recombinant protein SARS-CoV-2 vaccine. The vaccine contains the recombinant nanoparticle displaying RBD of SARS-CoV-2 Spike (S) protein. GBP510 is composed of a two-component nanoparticle. Component A, expressed in Chinese hamster ovary cells, contains the RBD in its structure, and component B, expressed in *E. coli*, forms a pentameric nanoparticle structure. The vaccine is to be given with an AS03-adjuvant, which is to be mixed at the time of use. The vaccine is intended to be given as two doses IM with a 4 week interval between doses.

Methods

The clinical safety of GBP510 has been evaluated in two clinical trials: a phase 1/2 first in human dose-finding trial, GBP510_002, and the pivotal phase 3 trial, GBP510_003. Furthermore, a supportive study, GBP510_001, evaluated the SARS-CoV-2 RBD nanoparticle, a recombinant protein given together with aluminium hydroxide. However, as the study GBP510_001 valuated non-adjuvanted and AlOh-adjuvanted SARS-CoV-2 nanoparticle formulations, data from this study are not considered informative for the safety of GBP510. Hence, GBP510_001 is not considered in the safety section for this AS03-adjuvanted protein nanoparticle vaccine.

The Applicant has presented pooled safety data from the GBP510_002 and GBP510_003 studies, which forms the basis for evaluating and discussing safety.

Overall, the methods for the collection of safety data appear to be appropriate. The Applicant is requested to provide the definition of a Serious Adverse Event maintained in the trials (OC).

Exposure

The safety database includes 3133 subjects who received GBP510 [25 µg adjuvanted with AS03 vaccine candidate (1 squalene (10.69 milligrams), DL-α-tocopherol (11.86 milligrams) and polysorbate 80 (4.86 milligrams))]. These subjects were included in 2 clinical trials, GBP510_003 (n=3029) and GBP510_002 (n=104).

No information could be found on actual follow-up time available since the first and second dose for these 3133 subjects. The Applicant should provide an overview of the follow-up time since the first and second dose (days, weeks, months, median and mean) for the pooled safety database as well as for the two trials separately. (OC) The Applicant is requested to provide the mean and median time between dose 1 and dose 2 for the entire safety database and per study separately. (OC)

Furthermore, additional follow-up time has been accumulated since the completion of the CSRs and the Applicant intends to provide 6 months of safety follow-up data no later than D120. The Applicant is invited to present an updated pooled safety analysis if available (OC). If doing so, please also include updated information of follow-up time (see above).

Whilst the safety database is minimal, with 3003 subjects who received 2 doses of the final vaccine formulation and dose, it is sufficient in size to exclude (serious) adverse events which may occur in approximately 1 in 1,000 vaccinees. As outlined in the *Considerations on COVID-19 vaccine approval*, most adverse reactions to vaccines occur within 4-6 weeks from vaccination, and it is expected that at least 6 weeks post-vaccination, safety data for the entire safety database will be available for review.

Participants included in the safety database were relatively young and generally healthy, with few subjects with underlying medical conditions.

Adverse events

The number of SAEs of the pooled safety analysis is not in agreement with the numbers reported in the individual CSRs. Therefore, the Applicant should double check and correct all tables in the pooled safety analysis where necessary and also check the frequencies in the text where the assessor computed the frequencies. (OC)

Due to the difference in randomisation ratios between cohorts, the applicant should provide the safety summaries for cohort 1 and cohort 2 separately. The Applicant should comment on any discrepancy observed between cohorts. (OC)

Solicited AEs

The most common solicited local reaction was injection site pain, reported by 67% of persons in the GBP510 arm and 49% in the ChAdOx1-S arm. Overall, local reactions were reported more often in the GBP510 arm compared to the ChAdOx1-S arm, both after the first as after the second vaccination although differences were more pronounced after the second vaccination. Most local reactions were mild to moderate, and 1.5% in the GBP510 arm reported severe injection site pain.

The most common solicited systemic reactions were fatigue, myalgia and headache, which were reported by 33%, 32% and 31% of participants in the GBP510 arm vs 33%, 31%, and 33% in the ChAdOx1-S arm.

Rates of systemic reactions after any dose were similar, if not higher, in the placebo arm, where 49%, 31% and 34% reported fatigue, myalgia and headache, respectively, compared to 33%, 32% and 31% in the GBP510 arm. This results from the higher reporting of reactions observed in Korean centres. GBP510_002, in which the placebo arm was included, was conducted in South Korea. In this study, reactions in the active arms were reported more frequently compared to the placebo arm, with rates highest in the 25 ug adjuvanted treatment arm where for example, almost 80% reported myalgia after any dose. This implies that the placebo rates are maybe less relevant in the pooled analysis.

Grade 3 (severe) systemic reactions were reported by similar proportions in the GBP510 and ChAdOx1-S arm, with most reactions being mild to moderate. Systemic reaction fever was reported more commonly in the GBP510 arm after the second vaccination (11%) compared to the first vaccination (6%). Other systemic reactions were reported at a similar frequency for both vaccinations.

No information on the duration of reactions could be found; this should be provided (OC).

Unsolicited AEs

Due to the low number of participants in the placebo group relative to the active arms, direct comparisons with the placebo group are of little value as the observation that no AEs in a particular SOC or PT were reported may be due to the fact that the numbers were too low to detect such AEs.

Most unsolicited AEs were within the SOC of *Infections and infestations* and concerned either COVID-19 or suspected COVID-19. There are no clear patterns of other adverse events reported significantly more often in the GBP510 arm than in the ChAdOx1-S arm. Regarding the AEs considered related by the investigator, there are no large or notable imbalances between study arms.

Several known ADRs for Vaxzevria (ChAdOx1-S) were reported at a similar or higher frequency in the GBP510 arm (highlighted in yellow in Table 27). Based on this, the following ADRs should be included in the labelling of GBP510 as well: *dizziness, hypoaesthesia, paraesthesia, somnolence, injection site pruritis, injection site warmth, injection site bruising, abdominal pain, chills, asthenia, decreased appetite, urticaria, rash, pruritis and pain in extremity*.

Of these, only urticaria is not included in the Table 4.8 of the SmPC. The Applicant should list urticaria. (OC)

Despite the low frequency and limited information on the reports of *lymphadenopathy* and *hyperhidrosis*, considering these are known ADRs for ChAdOx1-S and were observed in the GBP510 arm, and considering hyperhidrosis events were considered related to GBP510 by the investigator, it is agreed to include them in the ADR table in 4.8 of the SmPC.

The inclusion of the following additional AEs are proposed in section 4.8 of the SmPC is questioned by the assessor, and the Applicant should provide clear justification for inclusion or remove these from the table in 4.8 (OC):

- Dyspepsia: same incidence as in ChAdOx1-s arm, not included in SmPC of ChAdOx1-s; therefore, no clear reason for inclusion, and it should be removed.
- Oropharyngeal pain: same incidence as in ChAdOx1-s arm, not included in SmPC of ChAdOx1-s; therefore, no clear reason for inclusion, and it should be removed.
- Cough: same incidence as in ChAdOx1-s arm, not included in SmPC of ChAdOx1-s; therefore, no clear reason for inclusion, and it should be removed.
- Back pain: same incidence as in ChAdOx1-s arm, not included in SmPC of ChAdOx1-s; therefore, no clear reason for inclusion, and it should be removed.
- Groin pain: there were 4 reports in the GBP510 arm with an incidence of 0.13%. Although there were no reports in the comparator arms the incidence is too low to exclude chance finding (for example, skin laceration also was reported more frequently in the GBP510 arm (n=5) but clearly not related to vaccination – the study did not have sufficient power to detect differences in AEs with this low frequency between arms). Further, an underlying mechanism is unclear. Therefore this should be removed.
- Pain: this is non-specific and may cover the terms 'pain in extremity' or 'injection site pain', which are both proposed to be included in the SmPC. Unless it is clear that there is an additional type of pain caused by the vaccine, this should be removed.

There was a case of somnolence in the GBP510 group that was considered related. Due to previous association between an AS03 adjuvanted H1N1 vaccine and the occurrence of narcolepsy, a complete case description for the event of somnolence is requested (OC).

As it is unclear how the Applicant determined the frequency of ADRs included in the table in section 4.8, the Applicant should provide an explanation and justification (OC).

Finally, it is noted that the Applicant is proposing to include chest pain and palpitations in the table in section 4.8 of the SmPC. As the incidence is not different to the incidence observed in the ChAdOx1-S arm, and these AEs are not included in the SmPC of ChAdOx1-S as adverse drug reactions, relatedness is unclear. However, considering the number of ADRs reported concerning chest pain, chest discomfort as well as palpitations, and considering the investigator suspected relatedness, the Applicant is requested to provide more information on these events. (OC)

With regards to the AESIs, the Applicant has only provided a discussion of AESIs that were identified as SAEs (although the AKI was not identified as an SAE, it was reported via an SAE form). The Applicant is requested to confirm that non-serious adverse events that fall within the list of AESIs were collected throughout the entire study period. An overview of all non-serious adverse events which fall within the list of AESIs (either COVID-19 related or pIMD) occurring per treatment arm is requested.(OC)

Deaths and other SAEs

There were two deaths during the clinical development of GBP510. Both occurred in study GBP510_003, one in the GBP510 arm due to a brain neoplasm and one in the control arm due to cardio-respiratory failure. Both were considered not related to the treatment. There was no information on the death in the GBP510 treatment arm due to brain neoplasm within the CSR or in the patient listings. The Applicant is requested to provide the CRF for this death and a discussion on possible relatedness. (OC)

The SAE of Glomerulonephritis rapidly progressive was assessed to be related to vaccination with GBP510 by the investigator and is listed in section 4.8 of the SmPC as an ADR. The data provided, however, do not permit a clear conclusion on the diagnosis and potential cause and relation to GBP510. The differential diagnosis is broad, including post-infectious glomerulonephritis, auto-immune (rapidly progressive) glomerulonephritis alone or as part of a systemic disease, drug-related tubulo-interstitial disease (either GBP510, or another drug like the antibiotics prescribed), TMA, rhabdomyolysis, paraprotein related, or a primary kidney disease. More information is needed to draw a clear conclusion regarding the diagnosis, examine potential relatedness and underlying pathology and better characterise this potential risk.

As the Applicant considers that this severe event is related to vaccination, considering the severity of the event, the timing and immune pathology, the uncertainty around this single case and the diagnosis constitutes a major issue and renders the B/R of GBP510 negative. The Applicant should provide additional information on this event: clinical presentation, including blood pressure and clinical signs of vasculitis; laboratory results, including the course of eGFR, proteinuria, and urine sediment, additional serologic testing, especially in case of glomerular hematuria and related to the findings of renal biopsy (complement, ANA, ANCA, anti-GBM, parameters of hemolysis, fragmentocytes, CPK, potentially blood cultures), and the result of the kidney biopsy. In addition, details on the treatment, including the dose of corticosteroids and other medication prescribed, is relevant. The Applicant is requested to provide details of the SARS-CoV-2 serostatus of this participant at baseline. Further, it is expected that the Applicant provides a thorough assessment and critical discussion of potential relatedness considering the underlying pathology, the potential mechanism, the timing (onset 3 days after immunisation), the epidemiology. A thorough review of the literature is expected in support of their discussion (OC).

There was an SAE of pneumonia in a participant in the GBP510 arm, with onset (first reported symptom: cough) 18 days after the second dose. The participant was hospitalised for 4 days. There are no details on treatment or diagnosis. The Applicant is requested to provide any available information regarding testing for SARS-COV-2 for subject 104-0020. (OC)

During the 6-month follow-up period in GBP510_002 an SAE of spontaneous abortion occurred in the GBP510 25 µg adjuvanted with AS03 group. Table 16.2.7.2 was not completely submitted (only 15 pages of the 104 pages were submitted, some text is in Korean) and details on this SAE could not be found. From the information in the section on pregnancy in the clinical safety summary it appears that the pregnancy started after exposure to the vaccine, but this should be confirmed. The Applicant is requested to provide the narrative for this SAE. (OC)

According to the information under SAEs there were 9 serious cases of COVID-19 in GBP510_003. According to the information under 'exploratory analyses' in the CSR (section 5.3, pg 165/211 and further), there were no severe or critical COVID-19 cases. This inconsistency should be explained. Further, the Applicant is requested to provide the narratives of the COVID-19 cases observed during the study duration. (OC)

Clinical laboratory findings

Haematology and clinical biochemistry values were assessed in phase 2 study GBP510_002. There was no shift between baseline and visit 7 (28 days post-dose 2) in haematology tests in participants who received GBP510 25ug with AS03. Considering blood chemistry, in the GBP510 25ug with AS03 the only changes vs baseline values were in 3 participants (2.9%) who had a shift from normal in triglycerides (2 increase, 1 decrease), compared with 1 participant (1.7%) in the placebo arm (increase). The available data make it unclear whether this could be a chance observation. The actual levels measured could not be found. The severity grading scale for blood triglyceride levels could not be found in the protocol (V4), possibly as these are not provided in the FDA guidance document on which the classification of severity is based. There was no change from baseline in blood cholesterol levels above normal. The clinical relevance of these transient changes is unknown. Finally, as the % with an increase was similar compared to the placebo group, this observation cannot be attributed to vaccination.

Safety in special populations

Whilst safety was to be analysed by sex, age and ethnicity/region, the tables referenced could not all be located or were incomplete (e.g. solicited reactions by sex), and no description with sufficient detail of these subgroup analyses was included in the Safety Summary and in the individual CSRs.

It is in particular relevant to have insight into the effect of region on safety as data mostly comes from outside Europe, and the relevance to the EU population needs to be demonstrated. It is pertinent to see the differences in reporting rates between a Korean and South East Asian populations. As in GBP510_003 no placebo was included, it is not known whether this is solely due to the vaccine or due to different reporting or experience. If anything, the relevancy of the rates of ADRs as determined in a mostly South East Asian population for the European population should be discussed and demonstrated. As there were >200 Caucasians included, likely all in European centres, a comparison between solicited reactions between Korean, European and South East Asian participants may be informative to this respect (Please also refer to: Extrapolation of results from clinical studies conducted outside Europe to the EU-population | European Medicines Agency (europa.eu), ICH E5 (R1) Ethnic factors in the acceptability of foreign clinical data | European Medicines Agency (europa.eu)).

To aid assessment, the Applicant is requested to present subgroup analyses for safety by age, sex, ethnicity and/or region based on the pooled safety dataset and provide the tables in word format. Ideally, safety data per subgroup should be presented in a single table for overall adverse events, solicited adverse events (local/systemic), unsolicited adverse events and serious adverse events (e.g. that a single table shows both the solicited systemic reactions in a single table for subjects 19-64 and 65 years or older side by side, a second table for both men and women side by side as well as a table for the different regions) (OC)

The Applicant is additionally requested to present the safety and reactogenicity by serostatus (OC).

Finally, the Applicant should provide the table of safety events by age group (older ages) as part of the answers to the day 120 LoQ. (OC)

Discontinuation due to AEs

In one participant in the GBP510 arm in GBP510_003, reactions to the vaccine resulted in the discontinuation of the trial. The Applicant is requested to provide an overview of adverse events that resulted in discontinuation of vaccination (i.e. AEs occurring after the first dose resulting in participants opting out of the second dose but not necessarily discontinuing the trial). (OC)

Additional safety data needed in the context of a Conditional MA

None.

3.3.9. Conclusions on clinical safety

Overall, the safety profile of GBP510 is characterised mainly by local and systemic reactions mild to moderate in severity. However, many issues are identified, which relate mostly to poor documentation of methods and safety findings as well as clarifications as to how these findings are included and reflected in the SmPC. Further, a single SAE of glomerulonephritis rapidly progressive occurred with onset 3 days after the first dose of GBP510, which was judged by the investigator and by the company as related to the study drug. Additional details are requested to understand the pathology better, including mechanism and possible relatedness.

The following measures are necessary to address the missing safety data in the context of a future Conditional MA:

None.

3.4. Risk management plan

3.4.1. Safety Specification

Summary of safety concerns

The Applicant proposed the following summary of safety concerns in the RMP:

Summary of safety concerns	
Important identified risks	
Important potential risks	Potential Immune Mediated Diseases (pIMDs) Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)
Missing information	Use in pregnancy and while breastfeeding Use in immunocompromised patients Use in frail patients with comorbidities (e.g. chronic obstructive pulmonary disease (COPD),diabetes, chronic neurological disease, cardiovascular disorders, autoimmune or inflammatory disorders) Interaction with other vaccines Long-term safety

3.4.1.1. Discussion on safety specification

The Applicant has presented an elaborate overview of the incidence and prevalence as well as the burden of SARS-CoV-2 globally up to April 2022. Further, an overview of treatment options and licensed vaccines are listed with a cut off of July 2022.

The non-clinical part of the safety specification contains more data than was submitted for evaluation. Please see non-clinical AR.

The Applicant states that known history of SARS-CoV-2 was an exclusion criteria, but that seropositive subjects were not excluded from the safety cohort of the phase 3 study. This is correct, and these can be therefore deleted from the list of populations not studies in the clinical trials. (OC)

Myocarditis/Pericarditis should be added as an important potential risk (OC).

Of note, Guillain-Barré syndrome is not an allergic reaction to vaccine and this should be corrected.(OC)

The Applicant has not considered any important identified risks. The Applicant has identified a single SAE of rapidly progressive glomerulonephritis (RPGN) which according to the Applicant may have been caused by the vaccine. There are at this moment many uncertainties around this case including around the diagnosis as well as potential relatedness; however, this cannot be excluded.

The description of pIMDs shows that this is foremost a theoretical risk associated with inclusion of an adjuvant, in this case AS03. pIMDs should be included in the list of AESIs and may be monitored post licensure through routine Pharmacovigilance. Therefore, the inclusion as an important potential risk should be further discussed. (OC)

With regards to the important potential risks: inclusion of VAED and VAERD is agreed.

Missing information as identified is largely in line with EMA guidelines (CoreRMP19) and take into account relevant missing populations from the clinical development programme. Patients with autoimmune or inflammatory disorders should be listed as a separate population (as they are not the same as frail patients). (OC)

3.4.1.2. Conclusions on the safety specification

Having considered the data in the safety specification,

The Rapporteur considers that the following issues should be addressed :

- Further justification for inclusion of pIMDs as an important potential risk is requested
- Myocarditis/pericarditis should be included as an important potential risk.
- Use in patients with autoimmune or inflammatory disorders should be included as Missing Information

3.4.2. Pharmacovigilance plan

1. Signal Detection and other routine pharmacovigilance activities

The Applicant stated that signal detection will be performed with qualitative and quantitative pharmacovigilance methods. The data sources, methods and frequency are described in below table.

Table. Signal Detection Activities

Activity/Data Source	**Frequency of Review**
Qualitative Data Review	
ICSR (Individual Case Safety Report) medical review of serious cases	Each business day
Review of signal notifications	Each business day
Literature review of Pubmed	Weekly
Line listing review of adverse event reports from the safety database	Weekly
Review of SK Bioscience's post-authorisation Safety Database, including all spontaneous and solicited ICSRs, Medicines and Healthcare products Regulatory Agency (MHRA), Eudravigilance Data Analysis System (EVDAS)1	Weekly
EVDAS Electronic Monitoring (eRMR) [1]	Bi-weekly
Aggregate review of SK Bioscience's Clinical Trial Database	Monthly
Review of Pharmacovigilance Risk Assessment Committee (PRAC) recommendations on signals1	Monthly
Quantitative Data Review	
Trends over time/frequency analysis	Bi-weekly
Disproportionality analysis using EVDAS	Bi-weekly
Observed versus expected (O/E) analysis	Monthly

[1]Applicable once product is authorised in the EU

Monthly Summary Safety Reports (MSSRs)

In addition to routine 6-monthly PSURs, the applicant will submit monthly safety reports containing a review of safety information received during the reporting interval, as well as cumulative data.

Summary of safety reports (SSR) complements the submission of PSURs and the need and periodicity of continuing the submission of the SSRs will be evaluated based on the post-marketing data after 6 months from marketing authorisation date. The proposed contents included in SSR are as follows:

- Interval and cumulative number of reports, overall by age groups and in special populations
- Interval and cumulative number of reports per HLT and SOC;
- Reports per EU country
- Exposure data based on administered doses whenever possible, stratified by region (and within the EU also by country), by age groups, gender, by first vs. second dose
- Safety-related changes to the reference safety information and actions taken in the interval

- List of ongoing and closed signals in the interval, including a summary of their evaluation; reviews of signals identified during the period or of safety topics identified by EMA and requested to be addressed in the MSSR
- Summaries of reported cases of selected AESIs and RMP safety concerns: report numbers and relevant cases, including Observed versus Expected (O/E) analysis (when possible)
- Fatal reports- numbers and relevant cases (considering co-morbidities and frailty), including O/E analyses (when possible), stratified by age groups.
- Medication errors, if a pattern of errors leading to harm is identified and/or risk minimisation activities are considered warranted
- Details of the search strategy, case definitions, and methodology for O/E analyses including source of background rates, risk windows, etc., as needed
- Risk/benefit considerations

In general, the proposed signal detection methods and the content of SSRs are endorsed.

It is noted that a list of AESIs is attached to the RMP which is more extensive than the EMA AESI list in particular related to the "List of potential Immune-mediated Diseases (pIMDs)". The list of pIMDs is considered too granular. The list may focus on the most relevant pIMDs (including narcolepsy). *OC*

The Applicant stated that exposure data will be provided to put ADR reports into context and to perform sound observed versus expected analyses. Whenever possible exposure data will be stratified by region/ country within the EU, age, gender, first and second dose. This approach is very much appreciated. The Applicant is kindly asked to specify the source to obtain exposure data (e.g. ECDC in the EEA). *OC*

For observed versus expected analyses also source of relevant background data should be mentioned. *OC*

The Applicant is reminded to use international agreed case definitions e.g. Brighton Collaboration case definitions (if available) to assess diagnostic certainty of adverse reactions reported in ICSRs. *OC*

The Applicant will perform as one signal detection method analyses of "Trends over time/frequency analysis", which is agreed upon. The applicant is kindly asked to provide some more information about the proposed analysis. *OC*

Traceability

To facilitate traceability of use of this vaccine, the SmPC includes instructions for Health Care Professionals (HCP) to record the name and batch number of the administered vaccine for each recipient.

The carton, which is the lowest saleable unit of the product, contains the product global trade identification number (GTIN), lot/batch number, expiry date and serial number printed as human readable information. The vaccine carton labelling also contains a scannable 2D barcode that provides the batch/lot number, expiry date and serial number.

Traceability is available for every shipping container of COVID-19 vaccine, which is fitted with a unique device that provides real-time monitoring of geographic location 24 hours per day, 7 days per week. Each device will also trace the batch/lot of the associated shipment. The device is activated prior to shipment and information is transmitted wirelessly to the SK bioscience at a predefined cadence until delivery to import location. Each shipment will be accompanied by a passive temperature datalogger.

Alarms for excursions (per predefined specifications) are programmed into the device. If the display on the device doesn't show an alarmed status, the vaccine can be received. If the display shows an alarmed status, the product needs to be stored in the appropriate temperature conditions upon arrival and the receiver needs to follow the SK chemical's instructions for reporting an alarmed shipment.

In addition to SmPC instructions for HCP to record the name and batch number of the vaccine and the carton labelling including scannable 2D barcode, it might be useful/necessary to provide also stickers to ensure full traceability. As the vaccine is a multidose vaccine several stickers per carton may be provided. The Applicant is asked to comment upon. OC

Routine PV activities: Specific AE follow-up forms for the following safety concerns

Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD): The VAED/VAERD questionnaire is attached to the RMP. The questionnaire covers relevant issues concerning potential VAED/VAERD case reports. The questionnaire is endorsed.

Summary of planned additional PhV activities from RMP

Study/Status	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing Authorisation				
Not applicable.				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not applicable.				
Category 3 – Required additional pharmacovigilance activities				
GBP510_002 (Stage 3) Ongoing	**[For stage 1]** Primary objective: To assess the reactogenicity and safety profile of GBP510 vaccines in healthy younger adults post each vaccination **[For stage 2]** Primary objective: To assess the immunogenicity of GBP510 vaccines in healthy younger and older adults post each vaccination **[For stage 3]** Primary objective: To assess the reactogenicity and safety profile of GBP510 vaccines in healthy younger and older adults post booster vaccination	pIMDs VAED Long term safety	Primary CSR Final CSR	09 February 2022 April 2023

GBP510_003 (Stage 2) Ongoing	**[For stage 1]** Primary objectives: To demonstrate that the immune response induced by 2 doses of GBP510 25µg adjuvanted with AS03 at 4-week interval in seronegative adults aged 18 years and older is superior / non-inferior to the immune response induced by 2 doses of ChAdOx1-S **[For stage 2]** Primary objectives: To demonstrate that the immune response against the wild-type virus induced by a third dose of GBP510 25µg adjuvanted with AS03 at least 12 to 32 weeks post 2nd vaccination with GBP510 25µg adjuvanted with AS03 is non-inferior to the immune response induced by a primary series of GBP510 25µg adjuvanted with AS03 in Test group participants aged 18 years and older; To demonstrate that the immune response against the wild-type virus induced by a single dose of GBP510 25µg adjuvanted with AS03 at least 12 to 32 weeks post 2nd vaccination with ChAdOx1-S is non-inferior to the immune response induced by a primary series of ChAdOx1-S in Control group participants aged 18 years and older	pIMDs VAED Long term safety	Primary CSR Final CSR	30 May 2022 July 2023

Data Base Study In South Korea Incidence of AESI and safety evaluation study after GBP510 adjuvanted with AS03 vaccination: A large-scale medical information database research in connection with vaccine registration data and health insurance data • Status: Planned	To investigate the incidence of AESI in subjects vaccinated with GBP510 adjuvanted with AS03 and evaluate the potential causal association between adverse events and GBP510 vaccine through comparison of **observed/expected rates and self-controlled case series**.	pIMDs VAED AESIs for GBP510 adjuvanted with AS03 Use in immunocompromised subjects Use in frail subjects with unstable health conditions and comorbidities (e.g; chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders, autoimmune or inflammatory disorders) Interaction with other vaccines Long-term safety	Protocol submission Final CSR	July 2022 3rd quarter 2025 Milestones to be Updated in the protocol
Pregnancy Registry COVID-19 Vaccines International Pregnancy Exposure Registry (C-VIPER) Country: UK • Status: Planned	To evaluate obstetric, neonatal, and infant outcomes among women vaccinated during pregnancy with a COVID- 19 vaccine.	Use in Pregnancy	Protocol Submission Progress reports Final CSR	3months after post-authorisation Annually from 2023 by 2027 2028 Milestone to be updated in the protocol

PASS UK Post- Authorisation Safety Study Using the Clinical Practice Research Datalink (CPRD) • Status: Planned	To evaluate whether there is an increased risk of pre-specified safety outcomes of interest following vaccination with the SKYCOVION COVID-19. To describe and characterise the safety profile of the SKYCOVION COVID-19 vaccine. To evaluate whether the risk of pre-specified safety outcomes of interest following vaccination with the SKYCOVION COVID-19 vaccine differs by characteristics such as age, sex, race/ethnicity, comorbidities/coinfections, prior COVID-19 infection, concomitant vaccinations, concomitant medications, and/or other characteristics	AESIs for GBP510 adjuvanted with AS03 Use in immunocompromised Subjects Use in frail subjects with unstable health conditions and comorbidities (e.g; chronic obstructive pulmonary disease (COPD), Diabetes, chronic neurological disease, cardiovascular disorders, autoimmune or inflammatory disorders) Interaction with other vaccines Long-term safety	Protocol Submission Progress reports Final CSR	3months after post-authorisation 12 and 24 months following the first date of GBP510 adjuvanted with AS03 vaccine administration in the UK or the approval of the study protocol, whichever comes later 36 months following the first date of GBP510 adjuvanted with AS03 vaccination Milestone to be updated in the protocol
Data Base Study In **South Korea** A Retrospective, Cohort Observational Study to Evaluate Vaccine Effectiveness of GBP510 Adjuvanted with AS03 • Status: Planned	To evaluate vaccine effectiveness of primary series and booster dose of GBP510 adjuvanted with AS03 against COVID-19 infections including severe and death cases, using Korean national COVID- 19 database	Not applicable	Protocol submission Final CSR	2nd quarter 2023 4th quarter 2023

PRAC Rapporteur Assessment Comment:

The planned effectiveness studies are endorsed.

Planned post-authorisation studies

Additional post-authorisation safety studies (PASS) will be conducted to investigate important identified and potential risks as well as missing information which was not evaluated in the GBP510 adjuvanted with AS03 clinical trials.

A. Database Study in South Korea - Incidence of adverse events of special interest (AESI) and safety evaluation study after GBP510 adjuvanted with AS03 vaccination-A large-scale medical

information database research in connection with vaccine registration data and health insurance data.

The objectives of this study are to investigate the incidence of AESI in subjects vaccinated with GBP510 adjuvanted with AS03 and to evaluate the potential association between adverse events and GBP510 vaccine.

Two methods are planned for this study to assess the risk of select AESIs: a self-controlled case series (SCCS) to compare the incidence rate ratio for the select acute AESIs within a prespecified risk window following GBP510 adjuvanted with AS03 with incidence during control window, and a prospective cohort study design to assess incidence of select AESIs and to analyse observed/expected rates for selected AESIs. Expected rates confirmed in the literatures will be used. The source population will comprise all individuals who were vaccinated with 1st and/or 2nd dose of primary series and who registered in National Health Insurance Service (NHIS) customized database linked to Korea Disease control and Prevent Agency (KDCA) vaccination registration data from 1 year before the first vaccination date with GBP510 adjuvanted with AS03 to 31 December 2023. The exact size of the population captured in the database will be monitored and reported in the study reports.

Milestones: The draft study protocol is planned to be submitted 3months following receipt of first regulatory authorisation in the UK or the EEA. The final Report estimated submission date is 3rd quarter 2025.

The Applicant provided a study synopsis. In general, the study design is acceptable although details need to be provided with the submission of the study protocol. The applicant committed to provide the draft study protocol within 3 months following receipt of the first regulatory authorisation in the UK or EEA. This is in principle acceptable, if 'draft study protocol' means that it is mature for review by PRAC.

B. COVID-19 Vaccines International Pregnancy Exposure Registry (C-VIPER)

The study is designed to estimate

a. the risk of obstetric outcomes (spontaneous abortion, antenatal bleeding, gestational diabetes, gestational hypertension, intrauterine growth restriction, postpartum haemorrhage, fetal distress, uterine rupture, placenta previa, chorioamnionitis, Caesarean delivery, COVID-19) and

b. the risk of neonatal outcomes (major congenital malformations, low birth weight neonatal death, neonatal encephalopathy, neonatal infections, neonatal acute kidney, preterm birth, respiratory distress in the new-born, small for gestational age, stillbirth, COVID-19). Infants will be followed up during the first 12 months of life.

Pregnant women exposed to single (homologous) or mixed (heterologous) COVID-19 vaccine series from 30 days prior to the first day of the last menstrual period (LMP) to end of pregnancy and their offspring will be included in the registry study. Data in pregnant women and their off-spring relative to a matched unexposed reference group who received no COVID-19 vaccines during pregnancy will be evaluated.

The study population includes 2 cohorts of pregnant women 18 years of age and older collected in the United Kingdom and matched by gestational age (2 weeks):

- Cohort 1: pregnant women exposed from 30 days prior to the first day of the LMP to end of pregnancy to at least one dose of GBP510 adjuvanted with AS03. These participants are enrolled as part of the C-VIPER.
- Cohort 2: pregnant women unexposed to a COVID-19 vaccine during pregnancy. These participants are enrolled through the Pregistry International Exposure Registry (PIPER) with the

same methods as those in Cohort 1. Women vaccinated before 30 days prior to the first day of the LMP are eligible for inclusion.

Pregnancy data will be collected at enrollment, monthly, and at the end of pregnancy. Liveborn infants are followed-up and data will be collected at birth and then every three months until 12 months of age. Information will be obtained directly from the participant.

Milestones: The draft study protocol is planned to be submitted 3 months following receipt of first regulatory authorisation in the UK or EEA.

Progress reports are planned for submission every 12 months following the first date of vaccine administration in the UK from 2023 by 2027. A final study report is planned for submission 12 months after study completion in 2027 but the submission date would be changed according to the regulatory approval date in the UK or EEA.

The Applicant provided a study synopsis of the planned registry study. In general, the proposed pregnancy study is endorsed. The robustness of the study results will depend on the level of exposure of SKYCOVION in pregnant women administered the vaccine in the UK. The matched control will consist of unvaccinated pregnant women. Considering that the overall majority of the population has already been vaccinated in the UK, the robustness of results will be largely dependent on the exposure of the vaccine in pregnant women in the UK. The Applicant is asked to comment on the feasibility of the study. ***OC***

It is expected that additional data in pregnant women may also be obtained from the secondary data analysis in South Korea. The submission time line for the draft study protocol is endorsed.

C. United Kingdom Post-Authorisation Safety Study Using the Clinical Practice Research Datalink

The objectives of the proposed study are:

1. To evaluate whether there is an increased risk of pre-specified safety outcomes of interest following vaccination with the SKYCOVION COVID-19 vaccine using a self-controlled design.
2. To describe and characterise the safety profile of the SKYCOVION COVID-19 vaccine
3. To evaluate whether the risk of pre-specified safety outcomes of interest following vaccination with the SKYCOVION COVID-19 vaccine differs by characteristics such as age, sex, race/ethnicity, comorbidities/coinfections, prior COVID-19 infection, concomitant vaccinations, concomitant medications, and/or other characteristics.

Two methods will be used to assess the risk of selected AESIs. A self-controlled case series (SCCS) to compare the incidence rate of safety outcomes of interest within a pre-specified risk window following the SKYCOVION COVID-19 vaccination with incidence during all control window following the vaccination within the same individual. A retrospective cohort study design where SKYCOVION COVID-19 vaccinated subjects and reference cohort (subjects vaccinated with other COVID-19 vaccines) are compared for occurrence of safety outcomes of interest.

The comparison cohort will be matched to the SKYCOVION cohort using frequency matching or propensity score matching. Matching can be done based on relevant covariates such as calendar time from the date of vaccination, age, sex, and comorbidities including COVID-19 infection during the baseline period, which will be defined as 365 days prior to the vaccine administration date (i.e., index date).

Milestones: The draft study protocol is planned to be submitted 3 months following receipt of first regulatory authorisation in the UK or EEA. The progress reports will be submitted at 12 and 24 months following the first date of GBP510 adjuvanted with AS03 vaccination in the UK or the approval of the

study protocol, whichever comes later. A Final study report is planned for submission at 36 months following the first date of GBP510 adjuvanted with AS03 vaccination in the UK. The detailed milestones will be included in the protocol.

PRAC Rapporteur Assessment Comment: In general, the study design is endorsed. The Applicant submitted a study synopsis. The timeline for the submission of the study protocol is acceptable.

D. A retrospective, observational cohort study to evaluate vaccine effectiveness of SKYCovion

Study objective is to evaluate vaccine effectiveness of a primary series and a booster dose of SKYCovion against COVID-19 infections including severe and death cases in Korean population aged 18 years and older, using the national COVID-19 database. This is a retrospective observational cohort study.

Study population: Cohort 1 includes Korean who have received a primary series of SKYCovion during the study period as an exposure group and Koreans have never received any dose of COVID-19 vaccination as a control group. Cohort 2 includes Koreans who have received a booster dose of SKYCovion as an exposure group and Koreans who have received a primary series of any COVID-19 vaccines as control group as a control group.

SKYCovion is intended to use the national COVID-19 database provided by KCDA and NHIS to search for COVID-19-related information from eligible individuals. According to the study synopsis data from four different databases will be linked: the 'Confirmed COVID-19 DB', 'COVID-19 vaccination DB', 'COVID-19 death DB' and 'Medical treatment DB'. After gaining approval to use the database for this study, the variables related to the COVID-19 information and demographics of individuals identified during the observation period will be provided in an analysed form.

Milestones: The draft study protocol is planned to be submitted in 2nd quarter 2023 and a final study report is planned in 4th quarter 2023.

In general, the study design is endorsed. *OC* The Applicant plans to submit the draft protocol in the 2nd quarter 2023 and the final in the 4th quarter 2023, which appears to be rather late. *OC* The Applicant is asked whether an additional effectiveness study based on European data would be feasible. The Applicant is asked to discuss different options. *OC*

Overall conclusions on the PhV Plan

In general, the Pharmacovigilance Plan is considered acceptable. There are questions related to traceability, use of exposure data, observed versus expected analyses. The applicant presented a list of AESI to be used for routine pharmacovigilance. In particular the list of potential immune-mediated diseases may be too granular (even considering the use of a strong adjuvant such as AS03).

The Applicant proposed three PASSs, based on data sources in South Korea and the UK. The Applicant committed to submit the draft protocols within 3 months of marketing authorisation in UK or EEA. Details of the study design and conduct will be discussed once the draft protocols will be submitted.

The PRAC Rapporteur, having considered the data submitted, is of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The PRAC Rapporteur also considered that routine PhV remains sufficient to monitor the effectiveness of the risk minimisation measures. *3]*.

Plans for post-authorisation efficacy studies

Summary of Post authorisation efficacy development plan

The Applicant proposes to perform an effectiveness study by data linkage of 4 different South Korean databases. It is understood that for the time being it is not quite clear whether the Applicant may get access to these data sources. The milestones concerning this study (final study protocol Q4 2023) are not very timely.

Due to some differences in epidemiology, it would be appreciated if an additional effectiveness study would be performed in Europe. The Applicant is kindly asked to discuss option for the conduct of an effectiveness study in Europe.

3.4.3. Risk minimisation measures

Routine Risk Minimisation Measures

The Applicant proposes routine risk minimization measure.

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	**Routine risk minimisation activities**
Important identified risks	None
Important potential risks	
PIMDs	**Routine risk communication:** None **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** None
Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD)	**Routine risk communication:** None **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** None
Missing information	

Use in pregnancy and while breastfeeding	**Routine risk communication:** Section 1.3.1 **SmPC section 4.6 and** Section 1.3.1 **PIL section 2** **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** None
Use in immunocompromised patients	**Routine risk communication:** Section 1.3.1 SmPC section 4.4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** None
Use in frail patients with comorbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders, autoimmune or inflammatory disorders, autoimmune or inflammatory disorders)	**Routine risk communication:** None **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** None
Interaction with other vaccines	**Routine risk communication:** Section 1.3.1 SmPC section 4.5 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** None

Long-term safety	**Routine risk communication:** None **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** None

Additional risk minimisation measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product. No additional risk minimisation measures are proposed.

Overall conclusions on risk minimisation measures

The PRAC Rapporteur having considered the data submitted was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

3.4.4. Conclusion on the RMP

The CHMP and PRAC considered that the risk management plan version 1.0 could be acceptable if the Applicant implements the changes to the RMP as detailed in the endorsed Rapporteur assessment report and in the list of questions in section 6.3.

3.5. Pharmacovigilance

3.5.1. Pharmacovigilance system

It is considered that the pharmacovigilance system summary submitted by the Applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

3.5.2. Periodic Safety Update Reports submission requirements

The active substance is not included in the EURD list and a new entry will be required. The new EURD list entry uses the EBD or IBD to determine the forthcoming Data Lock Points. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The Applicant did not request an alignment of the PSUR cycle with the international birth date (IBD).

The Applicant should indicate if they wish to align the PSUR cycle with the international birth date (IBD).

4. Non-Conformity with agreed Paediatric Investigation Plan

Not applicable.

5. Benefit risk assessment

5.1. Therapeutic Context

5.1.1. Disease or condition

The claimed indication for GBP510 vaccine is active immunisation of individuals ⩾18 years of age to prevent coronavirus disease 2019 (COVID-19).

COVID-19 is a disease caused by the novel coronavirus SARS-CoV-2. The clinical manifestation of COVID-19 is non-specific and variable. It can range from no symptoms (asymptomatic) to severe pneumonia and death. The disease burden is highest amongst subjects with increased age; however, all age groups are susceptible. Underlying health conditions such as hypertension, diabetes, cardiovascular disease, chronic respiratory disease, chronic kidney disease, immune-compromised status, cancer and obesity are considered risk factors for developing severe COVID-19.

The COVID-19 pandemic that has been declared by the WHO in March 2020 remains ongoing despite unprecedented efforts to control the outbreak.

5.1.2. Available therapies and unmet medical need

At the time of writing, several products have received marketing authorisation for the treatment of COVID-19. These encompass antiviral therapy (PF-07321332 / ritonavir, remdesivir), anti-inflammatory therapy (dexamethasone), IL-6 inhibitor (tocilizumab), IL-1 inhibitor (anakinra) as well as monoclonal antibodies directed against the SARS-CoV-2 spike protein (casirivimab/imdevimab, regdanvimab and sotrovimab). In addition, a combination of two monoclonal antibodies (tixagevimab/ cilgavimab) is authorised based on its ability to reduce the risk of COVID-19 infection.

These therapies have shown variable efficacy depending on the severity and duration of illness as well as against different variants of concern.

There are 6 approved vaccines for active immunisation against SARS-CoV-2 aiming to prevent COVID-19 disease: Comirnaty (EMEA/H/C/005735), Spikevax (EMEA/H/C/005791), Vaxzevria (EMEA/H/C/005675), JCovden (EMEA/H/C/005737), Nuvaxovid (EMEA/H/C/005808) and Valneva (EMEA/H/C/006019). For Comirnaty and Spikevax, adapted bivalent vaccines based on the original, Wuhan, strain and either an Omicron BA.1 or Omicron BA.4/5 strain have been approved recently.

5.1.3. Main clinical studies

The clinical development programme consists of 3 clinical studies, 2 investigating the immunogenicity and safety of GBP510 adjuvanted with AS03. These are the Phase 1/2 trial GBP510_002 (dose finding, with and without adjuvant) and the pivotal Phase 3 trial GBP510_003, in which the immunogenicity and safety of GBP510 has been assessed.

The Phase 3 study GBP510_003 is considered as main evidence and was designed to bridge immunogenicity results of GBP510 to CHAdOx1-S (AZD1222, Vaxzevria), a licensed COVID-19 vaccine with known efficacy. This study was designed to show the superiority of GBP510 in terms of inducing neutralising antibodies as well as non-inferiority for seroconversion rates of neutralising antibodies to infer vaccine efficacy in the absence of a currently established correlate of protection. The study consisted of 2 cohorts: Cohort 1 (immunogenicity) includes only participants with no history of SARS-CoV-2 infection and COVID-19 vaccination confirmed by a SARS-CoV-2 rapid antibody kit at screening, in cohort 2 (safety), participants were enrolled regardless of their serostatus. All vaccines were given in a two-dose schedule four weeks apart (as authorised for CHAdOx1-S) to evaluate the primary

outcomes two weeks after the second vaccination. No efficacy studies for GBP510 have been performed.

5.2. Favourable effects

Superiority GBP510/ChAdOx1-S neutralising GMTs. Superiority for GBP510 compared to ChAdOx1-S for the co-primary endpoint at 2 weeks post second dose was confirmed with a neutralising antibody GMT ratio (95% CI) of 2.9 (2.6, 3.2) in cohort 1 (wildtype strain).

Non-inferiority GBP510/ChAdOx1-S seroconversion. Seroconversion was defined as a ⩾4-fold increase in SARS-CoV-2-specific neutralising antibody titre levels between baseline and post-vaccination sample collection time points. Two weeks after the second vaccination, non-inferiority was confirmed with a lower bound of the 95% CI for the difference between the randomised groups of 7.7% in cohort 1 (wildtype strain).

Additional measures of humoral immunity. Primary outcomes based on neutralising antibodies are supported by secondary outcomes evaluating induction of S-protein specific binding IgGs (ELISA).

Additional measures of cellular immunity. The induced cell response appears Th1 skewed. No clear differences are observed between GBP510 and ChAdOx1-S.

Exploratory immunity against SARS-CoV-2 variants of concern. Neutralising antibodies were measured and detected against SARS-CoV-2 variants Delta and Omicron BA.1.

Exploratory humoral immunity data in SARS-CoV-2 seropositive individuals. A more pronounced humoral immune response in a limited set of individuals seropositive at baseline who received GBP510 compared to individuals seronegative at baseline became apparent.

COVID-19 incidence rates. The incidence rates of virologically-confirmed COVID-19 case in each group was 0.5% of participants in GBP510 group and 1.6% in ChAdOx1-S group after 14 days of 2nd vaccination. After any vaccination, it was reported in 2.1% of participants in GBP510 group and 3.3% in ChAdOx1-S group.

5.3. Uncertainties and limitations about favourable effects

No correlate of protection against COVID-19 exists. Neutralising activity of SARS-CoV-2 by hyperimmune sera is used as a surrogate *in vitro* marker to infer a protective effect, as this is thought to most closely reflect the *in vivo* scenario of antibody-mediated protection. However, no threshold for a protective effect has been established. The comparative approach of GBP510 to ChAdOx1-S with known efficacy is therefore essential for the interpretation of a potential protective effect of GBP510.

The **FRNT assay** is the bio-analytical assay employed for determination of neutralising antibody titre, which is pivotal to inference of efficacy. It is not clear from the provided information whether the FRNT assay is suitable for the intended purpose, and whether it is an appropriate substitute for the PRNT assay.

Primary analysis. The primary analysis was prespecified to be performed in seronegative subjects. It is not understood why adjustment for baseline was planned as the primary analysis in a baseline seronegative population. As randomisation has been stratified for centre and age-group, this should be appropriately accounted for in the primary analysis.

Control group. There are some unexpected findings in the control group. The response to ChAdOx1-S observed in a seronegative population in the registration trials was considerably higher than in study GBP510_003. In the baseline seropositive population, the response to ChAdOx1-S continued to increase after the second dose while there was a plateau in the neutralising antibody response after

the first dose in baseline seropositive persons in the registration trials. Further, subgroup analysis by ethnicity suggests a larger variation in responses in the ChAdOx1-S group between the three ethnic groups compared to the variation seen in the GBP510 arm.

Extrapolation to the European population. The data suggest considerable variation in response between ethnicities, which appears to affect the response in the two treatment groups differently. The relevance of the data for the European population is, therefore, not self-evident and should be further justified.

COVID-19 incidence rates. Incidence rates of virologically-confirmed COVID-19 between GBP510 and ChAdOx1-S should be interpreted with caution. There is only very limited information provided on how COVID-19 cases would be collected, how information on COVID-19 cases would be collected, how cases were classified as being symptomatic or asymptomatic, how testing was performed. This needs to be further detailed.

Immunity against currently predominant SARS-CoV-2 Omicron variant. Limited (research-grade) neutralisation data on GBP510-induced neutralisation against the delta and omicron BA.1 variant have been provided. Several concerns are raised regarding these data that need to be resolved before the data can be interpreted. Further, no data is available for the currently circulating dominant SARS-CoV-2 Omicron variants.

Cell mediated immunity. CMI was measured using a validated intracellular cytokine staining (ICS) assay as well as a validated FluoroSpot assay. For both assays, concerns were raised questioning the validation exercise. Until these are solved, the results of the CMI assays should be considered preliminary and interpreted with caution.

Persistence. Humoral immune response data from Phase 3 were provided up to 2 weeks after the second dose. Data from later time points have not been submitted yet. Humoral immune response data from Phase 1/2 suggest that the response 4 weeks after the second dose is substantially lower than the response 2 weeks after the second dose. This is observed both for binding antibodies as well as for neutralising antibodies.

Need and timing of booster after primary vaccination series. No data on booster vaccinations have been provided. The need and timing of a booster cannot be established based on the currently available information.

5.4. Unfavourable effects

The safety of GBP510 was characterised in two clinical trials, GBP510_002 and GBP510_0003, in which 3,133 participants were exposed to GBP510, and in which 3,003 participants received two doses. In GBP510_002, a placebo group was included which included 61 participants. GBP510_003 included an active comparator, ChAdOx1-S, to which 996 participants were exposed and 958 participants received the two dose vaccination course.

Solicited local reactions were reported at a higher incidence in the GBP510 group than in the ChAdOx1-S group after both the first and the second vaccination, although differences were more pronounced after the second vaccination. The most common solicited local reaction was injection site pain, reported by 67% of persons in the GBP510 arm and 49% in the ChAdOx1-S group. Local reactions were mostly mild to moderate (Grade 1-2), with <1% reporting severe (Grade 3) reactions after the first and second dose of GBP510.

The following adverse drug reactions were identified in addition to the solicited reactions: dizziness, hypoaesthesia, paraesthesia, somnolence, injection site pruritis, injection site warmth, injection site

bruising, abdominal pain, chills, asthenia, decreased appetite, urticaria, rash, pruritis, pain in extremity, hyperhidrosis, lymphadenopathy.

There were no deaths considered related to study vaccine, with similar rates between vaccine groups.

Overall, the incidence of **Serious Adverse Events** (SAEs) was low (<1%) and similar in the between the vaccine arms.

There was an SAE of Glomerulonephritis rapidly progressive following vaccination with GBP510, was assessed to be related to vaccination with GBP510 by the investigator and Applicant.

5.5. Uncertainties and limitations about unfavourable effects

The safety database is limited in size, with just over 3000 individuals exposed to two doses of GBP510. This is adequate to detect adverse events, which may occur 1 in 1000, however, not to identify more rare adverse events.

Long-term safety data are not yet available. The median follow-up duration since the first or second dose is unknown.

The duration of reactions was not reported. The relevance of the rates of ADRs as determined in a mostly Southeast Asian population for the European population is not clear.

The clinical safety database includes adults in good health. There is no information on the safety of GBP510 in frail individuals, individuals with autoimmune disorders, or individuals with significant underlying (unstable) disease (e.g. chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders). There is no data on the safety of GBP510 in pregnant women. These have been identified as missing information for the Risk Management Plan.

Available data do not raise a concern regarding vaccine-enhanced respiratory disease. The possibility of enhanced disease cannot be excluded with certainty and is listed as an important potential risk in the RMP.

Narcolepsy has not been reported in the context of this application. Nevertheless, due to the vaccine's composition using AS03 as adjuvant, narcolepsy is recommended to be closely monitored post-authorisation.

There are several uncertainties surrounding the event of Glomerulonephritis rapidly progressive, which occurred following vaccination with GBP510 in a young male with onset of 3 days after the first dose, and on last reporting was not yet resolved. The data provided, however, do not permit a clear conclusion on the diagnosis and potential cause and relation to GBP510. The differential diagnosis is broad, including post-infectious glomerulonephritis, auto-immune (rapidly progressive) glomerulonephritis alone or as part of a systemic disease, drug-related tubulo-interstitial disease (either GBP510, or another drug like the antibiotics prescribed), TMA, rhabdomyolysis, paraprotein related, or a primary kidney disease. More information is needed to draw a clear conclusion regarding the diagnosis, examine potential relatedness, and underlying pathology and better characterise this potential risk.

5.6. Effects Table

Table 25. Effects Table for GBP510 (data cut-off: 20 April 2022).

Effect	Short Description	Unit	GBP510	ChAdOx1-S	Uncertainties/ Strength of evidence	References
Favourable Effects						
Co Primary Endpoints	Superiority (Neutralising antibody GMT ratio GBP510/ ChAdOx1-S)	GMT ratio (95%CI)	2.9 (**2.6**, 3.2)		Superiority demonstrated Uncertainty around the FRNT assay	GBP510_003
	Non-inferiority (seroconversion rate difference between of GBP510 and ChAdOx1-S)	Difference in SCR rate (95%CI)	10.76% (95% CI: **7.68**, 14.32])		Non-inferiority demonstrated Uncertainty around the FRNT assay	GBP510_003
Unfavourable Effects						
Local solicited reactions	Injection site pain	%	67%	49%		
Systemic solicited reactions	Fatigue	%	33%	33%		
	Myalgia	%	32%	31%		
	Headache	%	31%	33%		
Serious AE	Glomerulonephritis rapidly progressive		1	0	Related to GBP510 according to investigator/ Applicant. Uncertainty around diagnosis and relatedness.	GBP510_003

Abbreviations: GMT=Geometric Mean Titre, Nab=Neutralising antibody
Notes: Seroconversion was defined as ⩾4-fold increase in SARS-CoV-2-specific neutralising antibody titre levels between baseline and post-vaccination sample collection time points

5.7. Benefit-risk assessment and discussion

5.7.1. Importance of favourable and unfavourable effects

The clinical development programme is based on an immunobridging strategy that compares the neutralising antibody response induced by the GBP510 vaccine with the authorised ChAdOx1-S vaccine

for which efficacy has been established. In addition, supportive data is submitted which allows further characterisation of the immune response. Incidence rates of virologically-confirmed COVID-19 between GBP510 and ChAdOx1-S have been collected but should be interpreted with caution given the lack of understanding on how cases have been collected.

The strategy of immunobridging, the comparator Vaxzevria (ChAdOx1-S) as well as the timepoints for the primary comparison all have been agreed in several scientific advices. Both predefined co-primary endpoints were met. GBP510 showed a superior neutralising antibody response and non-inferior seroconversion rate compared to ChAdOx1-S. Therefore, in principle, efficacy can be inferred.

However, it is unclear whether the FRNT assay is suitable for the intended purpose and is an appropriate substitute for the PRNT assay which is considered a critical caveat of the pivotal demonstration. An MO is raised requesting more information on the validation exercise as well as a comparison of the FRNT assay to another assay commonly used for the analysis of the neutralising antibody response.

Due to some uncertainty around the responses observed in the control arm, and unexpected observation in subgroup analyses which cannot easily be explained, several OCs are raised that need to be answered satisfactorily in order to get a better understanding of the data, and it's reliability before a final conclusion can be drawn.

The clinical trials have been conducted in a mostly Korean/Southeast Asian population, and only a few sites in Europe have been included. Therefore, the relevance of the overall clinical trial results for the European population needs to be considered. Furthermore, subgroup analysis by ethnicity revealed some unexpected observations. The data suggested a quantitative interaction between treatment and ethnicity. Therefore, the relevance of the data for the European population is not self-evident and should be further justified.

The current indication is for a primary series in adults 18 years of age and older. Whilst only few older adults aged ≥65 years of age were included in the clinical trials the pattern of neutralising antibody responses was consistent with that observed in the overall population: higher GMTs were seen in the GBP510 arm compared to the ChAdOx1-S arm. Given that it has been demonstrated that ChAdOx1-S is efficacious in older adults (albeit during earlier pandemic waves), it is reasonable to expect at least a similar level of protection afforded by GBP510 against symptomatic SARS-CoV-2 infection in older adults aged 65 years or older.

Given the wide availability of COVID-19 vaccines in Europe, including Wuhan-based vaccines but also variant-adapted vaccines, and the high vaccination coverage in Europe, there may not be a clear target population that will benefit from GBP510. In addition it remains unknown what level of protection may be expected against current circulating variants.

This should be balanced against the safety profile of GBP510, and the uncertainties around the safety profile. The incidence of solicited local and systemic reactions is as can be expected. Most events were mild to moderate, and only a few Grade 3 and higher reactions were reported. The safety database is however limited in size, with just over 3000 individuals exposed to two doses of GBP510, and an unknown duration of follow-up. There is no information on the safety of GBP510 in frail individuals, individuals with autoimmune disorders, individuals with a significant underlying (unstable) disease, or pregnant women. Also, the duration of solicited reactions was not reported.

Although the incidence of SAEs was low and similar between the two vaccine arms, there was an SAE of Glomerulonephritis rapidly progressive following vaccination with GBP510. This SAE was assessed to be related to vaccination with GBP510 by the investigator and Applicant. Additional details are requested to better understand the pathology, including the underlying mechanism and possible relatedness.

5.7.2. Balance of benefits and risks

The available clinical data for GBP510 may allow to infer efficacy and establish the benefits of preventing COVID-19 in immunised individuals 18 years of age and older. However, it needs to be established that the employed bio-analytical assay is suitable for determination of neutralising antibody levels. Further, several OCs are raised that need to be answered satisfactorily in order to get a better understanding of the data and it's reliability before a final conclusion can be drawn.

The Applicant has identified a serious safety concern. There are several uncertainties around the diagnosis and relatedness to vaccination which need clarification.

5.7.3. Additional considerations on the benefit-risk balance

A Conditional Marketing Authorisation, as requested by the Applicant, is not appropriate. Given the wide availability of COVID-19 vaccines in Europe, there is no unmet medical need for a Wuhan-based vaccine intended for primary vaccination that would justify a Conditional Marketing Authorisation. Although many outstanding issues have been identified including Major Objections on Quality and Clinical, if these issues are resolved the available data may be sufficiently comprehensive for a full MA.

Therefore, a full MA would be appropriate if all concerns can be resolved.

5.8. Conclusions

The overall benefit /risk balance of GBP510 is negative.