RECOMMENDATION FOR AN EMERGENCY USE LISTING OF SKYCOVIONE™ (COVID-19 VACCINE) SUBMITTED BY SK BIOSCIENCE Co., Ltd, REPUBLIC OF KOREA

Abstract

COVID-19 vaccine SKYCovione™ (GBP510), was submitted to the World Health Organization (WHO for evaluation under the Emergency Use Listing (EUL) by SK bioscience Co., Ltd. (SK bio) in the Republic of Korea. This vaccine contains a self-assembling, two-component nanoparticle (RBD-16GS-I53-50). 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. GBP510 is expected to have an enhanced ability to elicit a high immune response due to a molecular structure that enables the presentation of multiple highly homogeneous antigens. The vaccine is formulated as a sterile suspension containing RBD nanoparticles at a concentration of 25 µg/0.25 mL and it is accompanied with adjuvant AS03 which is to be mixed with GBP510 in 1:1 ratio at the time of use.

The clinical data presented were generated from three trials. The vaccine was shown to be safe and immunogenic. In the phase III trial that enrolled 4,033 subjects aged 18 years and above, the primary objective of the study was to demonstrate that the immune response induced by two doses of GBP510 25 µg adjuvanted with AS03 at a 4-week interval in baseline seronegative adults aged 18 years and older is superior (GMTs of neutralising antibodies) and non-inferior (Seroconversion [SCR] for neutralising antibodies) to the immune response induced by two doses of ChAdOx1-S at 2 weeks post second dose. Safety was included as a secondary objective.

Neutralising antibody GMT of 25 µg GBP510 with AS03 was superior to that of ChAdOx1-S, and SCR (percentage of subjects with ≥ 4-fold rise from baseline) of 25 µg GBP510 with AS03 was non-inferior to that of ChAdOx1-S. GBP510 with AS03 elicited a significantly ($P<0.0001$) greater immune response against both Delta (strain tested: GK clade; AY.69 lineage) and Omicron (strain tested: GRA clade; B.1.1.529 lineage) variants by the second week after Dose 2 than did ChAdOx1-S. The ratio of GMTs (GBP510 / ChAdOx1-S) observed for Delta and Omicron variants was 27.27 and 10.52, respectively. In addition, the vaccine showed adequate cellular immune response and no concern on the safety profile of the vaccine.

The proposed indication is: "Active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals ≥ 18 years of age." The Korea Ministry of Food and Drug Safety (MFDS) is the regulatory authority of reference and licensed the use of COVID-19 Vaccine (GBP510) on 29 June 2022.

This report was prepared by the product evaluation group (PEG) to be discussed by the technical advisory group for emergency use listing (TAG-EUL).

1 Introduction

1.1 Background

The current COVID-19 pandemic is unprecedented in the 21st century and the global response draws on the lessons learned from other disease outbreaks over the past several decades.

On 30 January 2020, following the recommendations of the Emergency Committee, the WHO Director-General declared that the outbreak constitutes a Public Health Emergency of International Concern (PHEIC). The International Health Regulations' Emergency Committee for COVID-19 met on Friday 27 January 2023. The WHO Director-General concurred with the advice offered by the Committee regarding the ongoing COVID-19 pandemic and determined that the event continues to constitute a PHEIC[1].

Globally, over 3.6 million new cases and over 25 000 deaths were reported in the period (27 February to 26 March 2023), a decrease of 27% and 39%, respectively, compared to the previous 28 days. Despite this overall downward trend, several countries have recently reported significant increases in cases. As of 26 March 2023, over 761 million confirmed cases and over 6.8 million deaths have been reported globally. Populations at risk include older adults and those with existing chronic medical conditions or underlying diseases.

Treatments of COVID-19 infection have been developed since the outbreak; however, these therapies have shown variable and limited efficacies depending on the progress of the disease and the appearance of variants or the virus. Multiple variants of the virus including the following five variants of concern (VOCs) were circulating globally: Alpha variant identified in United Kingdom (UK) in September 2020 (B.1.1.7), Beta variant identified in South Africa in May 2020 (B.1.351), Gamma variant identified in Brazil in November 2020 (P.1), Delta variant identified in India in October 2021 (B.1.617.2) and Omicron variant identified in multiple countries since November 2021 (B.1.1.529) (WHO 2022). Current evidence suggests the VOCs are more contagious and spread more easily than the original COVID-19 Wuhan strain. Most, if not all, variants, except for Omicron, have now been de-escalated in most of the WHO regions due to very low levels circulating in the community (e.g., in Europe as per ECDC 2022). The Delta variant is still listed as a variant of concern by WHO, alongside Omicron (WHO 2022). The Omicron variant is noted to have a reduced severity and increased immune evasion compared to the original strain.

1.2 COVID-19 vaccines

Shortly after SARS-CoV emerged at the turn of the 21st century, the spike (S) protein (particularly in its native conformation) was identified as the immunodominant antigen of the virus[2]. Once this putative vaccine target was identified, the next challenge was how to best generate an effective immune response to SARS-CoV-2. The characteristics of this response would include production of neutralizing antibodies, generation of a T-cell response, and avoidance of immune-enhanced disease[3].

[1] https://www.who.int/news/item/30-01-2023-statement-on-the-fourteenth-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-coronavirus-disease-(covid-19)-pandemic

[2] Du L, He Y, Zhou Y, et al. The spike protein of SARS-CoV—a target for vaccine and therapeutic development. Nat Rev Microbiol. 2009;7(3):226-236.

[3] Tseng CT, Sbrana E, Iwata-Yoshikawa N, et al. Immunization with SARS coronavirus vaccines leads to pulmonary immunopathology on challenge with the SARS virus. PLoS One. 2012;7(4):e35421.

Currently, a variety of different vaccines and vaccine platforms are authorized worldwide, such as mRNA vaccines, viral vector vaccines, inactivated and adjuvanted whole virus, and recombinant spike proteins.

Some of the current vaccine platforms favor the accelerated production of vaccines, while others may elicit a more rapid and robust protection. Therefore, vaccines that could exert protective immunity after a single dose remain preferred. However, the evolution of current pandemic has showed us that most of the current candidate vaccines for COVID-19 require two doses or more. There are now formulations based on more than one antigenic component.

1.2.1 The SKYCovione™ (GBP510) Covid-19 vaccine

This COVID-19 vaccine (GBP510) which 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. During manufacture, the two purified protein components are mixed in an established molar ratio (component A + component B) to drive the spontaneous assembly into the target nanoparticle structure.

SKYCovione™ (GBP510) is expected to have an enhanced ability to elicit a high immune response due to a molecular structure that enables the presentation of multiple highly homogeneous antigens. This potential to swap the presented antigen which is fused to the nanoparticle core through a linker, offers the possibility to generate different vaccines against different variants of SARS-CoV-2 as a mono or multi-valent vaccine. In fact, SK bio is reported to have also been developing variant strain vaccines containing nanoparticle expressing the RBD of other variants, which use the same technology.

The vaccine is formulated as a sterile suspension containing RBD nanoparticles at a concentration of 25 µg/0.25 mL and it is accompanied with adjuvant AS03 which is to be mixed with GBP510 in 1:1 ratio at the time of use. The vaccine is clear or slightly opalescent liquid that is provided as a multi-dose presentation. These are two multidose vials (antigen vial and adjuvant vial) that must be mixed before use. 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. GBP510 will induce immune responses against SARS-CoV-2 and has an enhanced ability to elicit an immune response owing to its molecular structure. Other ingredients of its formulation are sodium chloride, tromethamine, arginine, sucrose and water for injection.

The product is available in a colorless and transparent 5 mL type I glass vial with a rubber stopper and sealed with a flip-off cap. This adjuvanted vaccine is stored at 2°C to 8°C, making it compatible with standard vaccine distribution channels, which thus could aid in the further enhancement of the response to control this pandemic.

Based on a combination of a novel nanoparticle approach and an established technology of recombinant protein subunit, GBP510 would contribute to fulfil an unmet need, 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.

1.2.2 The adjuvant

AS03 is used as adjuvant in the present vaccine. The EUL applicant indicated that AS03 is selected to be used based on the available non-clinical and clinical data. AS03 is a squalene-based adjuvant, manufactured by GlaxoSmithKline (GSK). The applicant stated that the AS03 adjuvant has been used in GSK's Pandemrix, pandemic A/H1N1 influenza vaccine and Prepandrix®, pre-pandemic A/H1N1 influenza vaccine, through which its immune enhancement and safety have been proven.

AS03 adjuvant is composed of squalene, DL-α-tocopherol and polysorbate 80 (AS03 is a well-known adjuvant and already and used in vaccines prequalified by WHO. 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.

Adjuvanted AS03 boosts the immune response by increasing RBD-specific IgG and T-cell response through an antigen-sparing effect. 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. 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[4].

1.3 Emergency Use Listing

The EUL is a time limited risk-benefit assessment for emergency use of vaccines, medicines and *in vitro* diagnostics during a PHEIC when limited data are available and the products are not yet ready for licensure and WHO prequalification. As the EUL is time-limited in nature, the manufacturer is still expected to complete the development of the product and submit application for licensure and prequalification.

The issuance of an EUL for a product reflects WHO's recommendation for its use following a thorough scientific risk benefit assessment. However, each WHO Member State has the sole prerogative to allow the emergency use of a product under EUL within their country.

2 Assessment process

This COVID-19 vaccine (GBP510) is manufactured by SK Bio and was assessed under the WHO EUL procedure based on the review of data on quality, safety, efficacy, risk management plan (RMP) and programmatic suitability performed by WHO vaccine prequalification experts and evaluators from national regulatory authorities (NRAs) from different countries and regions.

[4] Safety of AS03-adjuvanted influenza vaccines: A review of the evidence. Vaccine. Volume 37, Issue 23, 21 May 2019, Pages 3006-3021.

The MFDS (Republic of Korea) is the NRA of record for this vaccine. GBP510 or SKYCovione™ batches will be released by MFDS.

3 Scientific Review

3.1 Quality overview

In accordance with the EUL procedure, the quality assessment by WHO of SKYCovione™, a vaccine developed for the prevention of COVID-19 caused by SARS-CoV-2 manufactured by SK bioscience included the evaluation of programmatic characteristics of the vaccine and its suitability for LMICs.

3.1.1 Drug Substance

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. Two components are held together by non-covalent interactions to form nanoparticle as a single antigen. Component A protein displays the receptor binding domain (RBD; which is the target antigen) of SARS-CoV-2 and is fused to a nanoparticle assembly domain (I53-50A). Component B (I53-50B) is naturally occurring bacterial enzyme that has been modified to be assembled with component A to form nanoparticle, which is considered as an active substance.

Component A displaying genetically fused RBD protein is expressed in Chinese Hamster Ovary (CHO) cells, and component B forming a nanoparticle structure is expressed in *E. coli*.

The intermediates component A and component B, and RBD nanoparticle drug substance (DS) are manufactured by SK Bio located at 150, Sanupdanji-gil, Poongsan-eup, Andong-si, Geongsang-bukdo, Republic of Korea. The site is also responsible for Quality Control, stability testing and release of component A, component B and RBD nanoparticle DS. Master Cell Bank (MCB), Working Cell Bank (WCB) used for component A and component B are manufactured and stored at this site as well. The applicant stated that the facility was inspected by the Medicines and Healthcare Products Regulatory Agency (MHRA) of the United Kingdom, and Good Manufacturing Practices (GMP) compliance was confirmed during that inspection.

Component A intermediate bulk is manufactured at 2000L scale. The manufacture of component A consists of upstream harvest process and downstream purification process. Each batch starts with thawing and plating one frozen vial of CHO WCB in a serum-free CD OptiCHO medium. Cells are cultivated in suspension in Erlenmeyer flasks and then in disposable bioreactors with increasing sizes. At each cell passage, cell viability and viable cell density are assessed. Glucose concentration and pH are also monitored during the cultivation in bioreactors. At the end of production, the culture broth that contains component A is harvested by continuous centrifugation, and tested for microbial bioburden, mycoplasma, mycobacterium, adventitious agents by in vitro assay, as well as mouse minute virus (MMV).

The downstream process starts with depth filtration followed by a detergent treatment step. Component A is purified by combination of three different types of chromatography, and concentrated. Conductivity

and pH are monitored for each chromatography step, and UF is controlled by transmembrane pressure. The downstream process also includes viral inactivation at low pH, and viral removal by nanofiltration prior to final concentration and sterile filtration. All the downstream process steps are performed at room temperature. Bioburden after each step, and filter integrity pre/post filtration are assessed. The sterile filtered component A is dispensed into 12 L sterile disposable bags and stored at or below -70°C.

Process validation Component A

Three consecutive process performance qualification (PPQ) batches of component A intermediate were manufactured at commercial scale. The release testing results for these batches met the specifications in place at the time and were consistent among the PPQ batches. At this stage RBD antigen content was not measured for component A intermediate. This is considered acceptable as the subsequent assembly process for RBD nanoparticle is performed based on the result of protein content, and the RBD antigen content is measured as part of QC release for RBD nanoparticle DS. The in-process control parameters (IPC) results met the acceptance criteria. The key process parameters for each batch were within the defined operating range.

Virus clearance was qualified using a scale-down model with 4 types of viruses representing gamma retroviruses, enveloped viruses, small size rodent derived viruses, and bovine derived viruses. Aged chromatography resin was accessed and comparable to new resins.

As the manufacturing site is GMP compliant upon MHRA inspection, the aseptic process and cleaning process are deemed to have been satisfactorily validated.

Component B intermediate bulk is manufactured at 750L scale. The manufacture of component B consists of upstream fermentation process and downstream purification process. Each batch starts with thawing and planting *E. coli* WCB from one frozen vial into flasks with kanamycin-containing media. The initial seed fermentation takes place in suspension and is then pooled into 1 000L stainless steel fermenter containing media, glycerol, kanamycin and antifoam agent. The culture harvest is transferred to a continuous centrifuge and the slurry is collected at a defined interval. The collected slurry is further centrifuged at high speed and the cell pellet is collected into a sterile disposable container, which is then stored at ≤ -70°C. At each fermentation stage, bacterial contamination and cell density are assessed as IPCs.

The downstream process starts with cell disruption using homogenizer upon thawing. The disrupted cells are treated with benzonase at room temperature followed by centrifugation. The pellet is washed twice at 4°C, and the final pellet is solubilized with buffer. After centrifugation, the supernatant containing the inclusion body is collected, filtered and loaded onto the column filled with DEAE resin for two runs of anion exchange (AEX) chromatography using negative mode for the first run and positive mode for the second run. Conductivity and pH are monitored. The eluate is concentrated and diafiltrated through TFF controlled by transmembrane pressure. Bioburden and endotoxin after second chromatography and after UF/DF, as well as filter integrity for TFF post filtration are assessed. The component B after final filtration is dispensed into 6L or 12L disposable bags and stored at or below -70°C.

Process validation Component B

Three consecutive PPQ batches of component B intermediates were manufactured at the commercial scale. The release testing results for these three batches met the specifications in place at time and were

consistent among the PPQ batches. The IPC results met the acceptance criteria. The critical process parameters (CPPs) and key process parameters (KPPs) for each batch were within the defined operating range.

Validation for the lifetime of chromatography was conducted and the data were provided.

As the manufacturing site is GMP compliant upon MHRA inspection, the aseptic process and cleaning process are deemed to have been satisfactorily validated.

Manufacturing of the Drug Substance
Component A and Component B are thawed at room temperature and filtered for 36 hours and filtered. Following re-quantification of the protein content, the volume of each component to be mixed is calculated based on the final protein concentration for the reaction, which is 1.5mg/mL, and the molar ratio. The assembly reaction is initiated by sequentially mixing component B, assembly buffer, 2% polysorbate 80 and component A. After 2 hours incubation at controlled temperature (23°C) with agitation, the solution is filtered, ultrafiltered and diafiltered. The UF/DF harvest is filtered and stored in aliquots in 6L or 12L disposable bags at -≤70°C.

Analytical Comparability between Clinical and Commercial (PPQ) Batches
All clinical and PPQ batches met the release specifications in place at the time of the submission of the EUL application. Antigen content levels were consistent throughout the clinical and commercial PPQ batches. It is noted that the particle size for the PPQ batches was slightly greater than that of Phase 3 batches. Although the particle size results for the PPQ batches were within the specification, trend analysis and comparability assessment to clinical batches are recommended once sufficient data become available. Regarding the characterization, the results were similar for peptide mapping, morphology examination by transmission electron microscopy (TEM) a suitable characterization technique for nanoparticles, and receptor binding analysis between the clinical and PPQ batches. It is noted that the DS bulk is composed of RBD nanoparticle and free component A. Data for the composition profile were available from two Phase 3 and three PPQ batches, for which the results were similar.

PPQ batches has demonstrated very low levels of residual process related impurities. The cumulative removal rate for the Phase 3 material and PPQ batches were below the quantitation limit.

In summary, the clinical and PPQ DS batches can be considered comparable based on the data provided at the time of the EUL application.

Container Closure System
The RBD nanoparticle DS bulk is filled into 6L and 12L sterile disposable ethylene vinyl acetate (EVA) copolymer bags and stored at ≤ -70°C. The bags are tested by the supplier in compliance with current compendial requirements. The applicant performs visual inspection, leak testing and gamma irradiation upon receiving the batch. The compatibility of the container closure system has been demonstrated through stability data.

Stability
The applicant is proposing a preliminary shelf-life of 12 months when the DS is stored at ≤ -70°C. Long-term stability studies were performed at ≤ -70°C for the clinical and commercial PPQ lots. Accelerated

stability studies were carried out at 2-8°C for a proposed 6-month duration for the Phase 3 and commercial PPQ lots. The 30-day and stressed stability study conducted at 23 - 27°C for the PPQ lots was completed. Appearance, pH, protein content and purity, antigen content, polysorbate 80, particle size, identity, endotoxin and sterility were tested at different time points.

The acceptance criteria for the long-term stability studies were the same as the release specifications. Long-term stability data up to 12 months and up to 3 months are available for the clinical lots and the PPQ lots, respectively. Accelerated stability data up to 3 months are available for the PPQ lots.

The currently available long-term stability results met the acceptance criteria for the claimed storage of 12 months at ≤ -70°C.

3.1.2 Drug Product

Recombinant COVID-19 subunit nanoparticle SKYCovione™, contains recombinant nanoparticles displaying the receptor binding domain (RBD) of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The antigen is composed of component A and component B, forming a self-assembled nanoparticle structure. It is a colourless, clear, or slightly opalescent liquid in a colourless and transparent 5 mL glass 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. An overfill is applied. The target fill volume is 3.10 mL.

The composition of the vaccine, before mixing with ASO3 includes buffers (e.g., tromethamine), stabilizers (e.g., sucrose). All formulation components are in compliance with the European Pharmacopeia, with the exception of the active ingredient (the subunit nanoparticles).

The qualitative composition of liquid AS03 is provided in the table below:

Ingredient	Function	Reference
Oil phase		
Squalene	Oil phase constituent	GSK monograph
D,L-α-tocopherol	Oil phase constituent immunostimulant	Ph. Eur and USP
Aqueous phase		
NaCl	Tonicity adjuster	Ph. Eur
WFI	Solvent	Ph. Eur
Na2HPO4	Buffering agent	Ph. Eur
KH2PO4	Buffering agent	Ph. Eur
Polysorbate 80	Surfactant	Ph. Eur
KCL	Tonicity adjuster	Ph. Eur

NaCl: Sodium chloride; Na_2HPO_4: Disodium phosphate; KH_2PO_4: Potassium dihydrogen phosphate; KCL: Potassium chloride. No novel excipients are used in the formulation.

Different adjuvant candidates were evaluated as part of the paharmaceutical development of this vaccine (e.g., aluminium hydroxide). However, AS03 was chosen as the final adjuvant to be used in SKYCovione™.

AS03 is a well-known adjuvant manufactured by GlaxoSmithKline plc., and already approved as an adjuvant of several other vaccines. Relevant information with regard to description and composition, specifications and testing and container closure system were provided. The type of information provided for the AS03 is acceptable.

The manufacturing process of GBP510 drug product (DP) is composed of preparation of formulation buffer, final bulk formulation, sterile filtration, aseptic filling, capping, visual inspection, labelling and packaging (vaccine + adjuvant).

Pharmaceutical development
Compatibility between the antigen and adjuvant was studied during product development. The following was studied:
Physicochemical properties
Biological characteristics
Dose dependent immunogenicity
Correlation of antigen content and *in vivo* immunogenicity
Receptor binding affinity

Production of drug product is as follows:

1. The formulation buffer is prepared in a disposable formulation bag contained in a formulation tank. Calculated amount of excipients are added and mixed with water for injection (WFI). The formulation buffer is filtered with 0.45/0.2 µm filter and is stored in a disposable bag at 2 – 8°C before further processing. The RBD nanoparticle DS contained in a disposable bag is thawed.
2. Thawed DS is transferred to a disposable formulation bag contained in a formulation tank and mixed with formulation buffer. The final bulk is filtered using a sterile filter and is kept in a disposable storage bag at 2 – 8°C before filling.
3. Filling is conducted in a Grade A area with restricted access barrier system (RABS). The disposable bag containing the final bulk is connected with an auxiliary container using tubes, and the final bulk is transferred into the auxiliary container along the tubes passing through sterile filters. While agitating in the auxiliary container, the final bulk is filled in vials with a target volume of 3.10 mL (3.20 g), using a vial filling machine.
4. The filled vials are immediately stoppered with rubber stoppers, which are then capped with flip-off caps. During the capping process, capping status and vial damage (vial neck, body and bottom) are monitored.
5. Capped vials are 100% visually inspected.
6. The filled vials are labeled and co-packed with the AS03 adjuvant.

Process validation
Three consecutive media fill batches were produced by three formulation and filing runs, which covered the routine process condition and batch size for DP production.

The DP manufacturing process has been validated through the production of three PPQ batches, manufactured in February 2022. The summary of PPQ results were provided in the submission; all results met the predefined acceptance criteria. The sizes of the PPQ batches cover the proposed batch size of

the commercial manufacturing process. The manufacturing parameters for the three batches, including the CPPs and KPPs, were within the pre-defined operating ranges.

The results of the in-process control, in-process monitoring, and in-process testing are in compliance with the acceptance criteria. In addition, samples taken at fixed intervals during filling showed consistent filling volume and weight; samples taken at the beginning, middle and end of the capping process also showed consistent protein content and antigen content. These results indicate that homogeneity is achieved during the formulation and filling process, and The DP manufacturing process is capable of producing DP with consistent quality.

Quality control

The specifications for quality testing of the final bulk, the drug product, before and after mixing with AS03, are provided and acceptable.

Analytical methods, specific for release and stability testing of the drug product, before and after mixing with AS03 are provided and found acceptable. The same analytical methods used for both the DS and DP are reviewed and found acceptable.

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 ASO3.
Analytical methods as well as method validation are provided and considered acceptable for the EUL purpose.

Container closure system

The vaccine is filled in a 5 mL Type I glass vial with a rubber stopper and sealed with a flip-off cap. The materials of construction for each component of the container closure system are listed in the table below:

Component	Characteristics	Quality Standard
Glass vial	USP Type I	Ph. Eur
Rubber stopper	Chlorobutyl	Ph. Eur
Flip-off cap	Aluminum seal Plastic (Polypropylene) flip-off cap	In-house

Container closure integrity test (CCIT) is performed as in-process control during the DP manufacturing process. The CCIT results for the three PPQ lots met the acceptance criterion.

Drug product stability

At the time of the EUL application, the proposed shelf-life for the vaccine was 12 months at the storage condition of 2°C - 8°C.

As per stability protocols, the planned stability studies on the clinical and PPQ batches include the following:

- Long-term (real time/real condition) storage condition at 5°C ± 3°C for 24 months;
- Accelerated storage condition at 25°C ± 2°C/60% RH ± 5% RH for 6 months;
- Stressed storage condition at 37°C ± 2°C/60% RH ± 5% RH for 7 days;
- In-use stability at temperatures of 5°C ± 3°C, 25°C ± 2°C, and 30°C ±2°C for 48 hours;
- An additional study at 5°C ± 3°C, 25°C ± 2°C, and 37°C ± 2°C for 24 hours.

The applicant uses the 12 months stability data for the clinical batches to support the proposed 12 months shelf-life for the commercial batches. The Phase 3 clinical batches are in the same multi-dose presentation as the commercial size PPQ batches.

The in-use stability data showed that after mixing with the adjuvant AS03, the product is relatively stable for at least 24 hours and no apparent antigen content degradation was observed. The applicant indicated that in order to minimize any loss of potency and safety, the product is recommended to be used immediately after mixing with the adjuvant. This information will be provided in the package insert. In the context of the EUL, this approach is found acceptable.

3.1.3 Adjuvant

SKYCovione™ is adjuvanted with AS03, which is a squalene-based adjuvant, manufactured by GlaxoSmithKline (GSK). The AS03 adjuvant is liquid oil in water emulsion and is filled in 3 mL Type I glass vial containers, sealed with 13 mm rubber stoppers and secured with flip-off caps.

Detailed descriptions of the container closure system as well as specifications for container parts were included in the EUL submission. The methods and release specifications for the adjuvant final containers are also provided.

3.2 Non-clinical overview

SK Bio has submitted to WHO for evaluation under the Emergency Use Listing procedure their new multi-injection vaccine, SKYCovione™ (GBP510). It is a recombinant protein subunit vaccine based on two-component self-assembling nanoparticle produced in CHO cells and *E. coli.* The vaccine targets the receptor binding domain (RBD) of SARS-Cov-2 spike protein and is adjuvanted with α-tocopherol oil-in-water emulsion, AS03. The two-component novel nanoparticle was developed by the Institute for Protein Design of the University of Washington, Seattle using its structure-based vaccine design techniques.[5]

Overall quality of the nonclinical dossier

The nonclinical dossier was of good overall quality and in general accordance with the relevant WHO regulatory guidelines for the nonclinical assessment of vaccines.[6] All pivotal nonclinical safety-related studies were conducted according to GLP. Detailed methodological information on the immunoassays and their statistical analyses were provided. Statistical analysis of these types of immune-hematological data is currently accepted scientific norm.[7] The submission consisted of a series of *in vitro* and *in vivo* primary

[5] Walls *et al.* (2020) Elicitation of potent neutralising antibody responses by designed protein nanoparticle vaccines for SARS-CoV-2.*Cell*. **183**: 1367.

[6] Guidelines on nonclinical evaluation of vaccine (WHO, 2005); Guidelines on nonclinical evaluation of vaccine adjuvants & adjuvanted vaccines (WHO, 2013);

[7] Reverberi, R. The statistical analysis of immunohaematological data. *Blood Transfusion* .2008; 6: 37-45.

pharmacodynamic studies, a series of safety pharmacology studies, four repeat-dose toxicity studies and a developmental and reproductive (DART) toxicity study. The use of a single sex (female) in some of the studies was inevitable and is acceptable from the point of few to keep to the principle of using minimum number of animals in these studies.

Summary of nonclinical pharmacological program of GBP510

Study Number	Testing Facility	Study Objective	Test/Animal model
Submitted as published papers – Walls *et al.*[8]	Institute for Protein Design University of Washington, Seattle	Structure & design of GBP510	*In vitro* Molecular Biology procedures
Unknown	Unknown	Binding affinity of GBP510 to ACE2 receptor	*In vitro* Biolayer Interoferometry
RSR510.04.03 Module 4.2.1.1	SK Bioscience, Jeonbuk National Univ. Zoonosis Research Institute, South Korea	Immunogenicity study of RBD-NP adjuvanted with alum and AS03 – NONCLINICAL BATCH	Balb/c mice
RSR510.04.04 Module 4.2.1.1	SK Bioscience	Immunogenicity study of GBP510 adjuvanted with alum and AS03 - CLINICAL BATCH	Balb/c mice
RSR510.04.03 Module 4.2.1.1	SK Bioscience, Jeonbuk National Univ. Zoonosis Research Institute, South Korea	Challenge study of RBD-NP adjuvanted with alum and AS03 – NONCLINICAL BATCH	hACE2 TG mice
RSR510.04.04 Module 4.2.1.1	SK Bioscience, Jeonbuk National Univ. Zoonosis Research Institute, South Korea	Challenge study of GBP510 adjuvanted with alum and AS03 – CLINICAL BATCH	hACE2 TG mice
RSR510.04.04 Module 4.2.1.1	Korea Research Institutes of Bioscience and Biotechnology, South Korea	Immunogenicity & challenge study of GBP510 adjuvanted with alum and AS03 in nonhuman primate - CLINICAL	Cynomolgus monkeys
RSR510.04.06 Module 4.2.1.1	SK Bioscience QuBest BIO Co. Ltd	Immunogenicity booster study of various forms of RBD-NP adjuvanted with AS03	Balb/c mice
RSR510.04.06 Module 4.2.1.1	SK Bioscience, BL3 Laboratory, Jeonbuk National Univ. Zoonosis Research Institute, South Korea	Challenge booster study of various forms of RBD-NP adjuvanted with AS03	hACE2 TG mice
RSR510.04.06 Module 4.2.1.1	Harvard University & University of Washington	Challenge booster study of various forms of RBD-NP adjuvanted with AS03 in non-human primate	Rhesus monkeys
Several (see Table 22 Section 2.2 this report)	Nonclinical Research Institute, ChemOn Inc. Suwon, South Koria	Safety Pharmacology: CNS, Respiratory & Cardiovascular systems (seven dedicated studies)	SD rats & Beagle dogs

3.2.1 Pharmacology

The nonclinical proof-of-concept immunogenicity and protective activity of SKYCovione® (AS03-GBP510) were evaluated in rodents (BALB/c mice, hACE2 transgenic mice and SD rats) and nonhuman primates (NHP; cynomolgus and rhesus monkeys). The animal models used were considered suitable for assessment of immunogenicity, efficacy and safety of the AS03-GBP510 vaccine. They are standard laboratory species used in vaccine studies, show immunological responses to the vaccine and have been used for assessment of immune responses to approved vaccines. All the studies used the IM clinical route of vaccine administration. None of the primary pharmacology studies were performed in compliance with GLP and were all conducted with good scientific principles considered appropriate for these types of studies. This is considered acceptable. No secondary pharmacology or pharmacodynamic drug interaction studies were conducted in line with nonclinical guidelines for vaccines. The nonclinical pharmacology program is adequate to investigate immunogenicity and efficacy of AS03-GBP510to support clinical development and use.

[8] Walls *et al.* (2020) Elicitation of potent neutralising antibody responses by designed protein nanoparticle vaccines for SARS-CoV-2.*Cell*. **183**: 1367.

In vitro pharmacodynamics

The Spike protein is a trimeric structure on the surface of the SARS-CoV-2 virus which binds to ACE2 receptors and is a key target for COVID-19 vaccines. SKYCovione® consists of a recombinant protein subunit vaccine, GBP510, based upon the SARS-CoV-2 S-protein RBD and includes the receptor binding motif which binds to the ACE2 receptor. To overcome the limited immunogenicity of the small monomeric RBD and increase its antigen-specific immune responses, the vaccine antigen GPB510 was designed to contain multiple distinct RBD epitopes by complexing it with nanoparticles. Displaying vaccine antigens in a multivalent fashion on nanoparticles is an established strategy to increase their immunogenicity.[9] This was the rationale for the use of the self-assembling protein nanoparticles from two distinct oligomeric protein components that act as a scaffold for multivalent antigen presentation.[10]

The structure and design of the active moiety of the vaccine, GBP510, was described in the paper submitted in the dossier (Walls *et al.* 2020).[11] The applicant gave a brief description of the structure which is summarised here. RBD nanoparticle is a 120 sub-unit complex with an icosahedral symmetry and a multivalent presentation, comprised of two components: Component A is expressed in CHO cells and contains a trimeric fusion protein displaying genetically fused RBD protein, while Component B is a pentameric protein purified from *Escherichia coli* that assembles with Component A to form the nanoparticle. The binding affinity for its target, the ACE2 receptor, was found to be approximately two orders of magnitude higher than that reported for SARS-CoV-2 S protein RBD expressed with a polyhistidine tag at the C-terminus (≤4.4x10^{-9} M).

The *in vitro* studies included characterization of immunoassays to qualify and quantify immune responses generated by RBD-NP/GBP510 vaccine candidates during subsequent non-clinical phases of development. The methods were developed, tested and standardised. These immunoassays include a validated ELISA using SARS-CoV-2 spike RBD as antigen to detect specific anti-RBD IgG antibodies and live virus neutralisation assays (plaque reduction neutralisation test or PRNT or cytopathogenic effect [CPE]-based assay). Preliminary studies were conducted to optimise VSV pseudovirus-based neutralisation assays (PBNA) for their capacity to detect neutralising antibodies against both wild-type virus and given variants of concern.

Immunogenicity

Early in the development of the SKYCovione® vaccine, different adjuvants were investigated to be used with the RBD-NP/GBP510, including AS03 an α-tocopherol-based oil-in-water emulsion, MF59 an oil-in-water emulsion composed of squalene, Alum-CpG1018 a TLR9 agonist formulated in alum and Alum (aluminum hydroxide).[12] Dose selection of these adjuvants was based on earlier studies conducted by others during the development of subunit vaccines against COVID-19.[13] Preliminary studies in mice showed that adjuvanted GBP510 induced higher antibody titers compared to non-adjuvanted GBP510 and the titers generated were higher with the AS03-adjuvanted vaccine. This was confirmed in later

[9] Brower *et al.* (2019) enhancing and shaping the immunogenicity of native-like HIV-1 envelope trimers with a two-component protein nanoparticle. *Nature Comm.* **10:**4272. Marcandalli *et al.* (2019) induction of potent neutralising antibody responses by a designed protein nanoparticle vaccine for respiratory syncytial virus. *Cell.* **177**: 1420.

[10] Bale *et al.* (2016) Accurate design of megadalton-scale two-component icosahedral protein complexes. *Science.* **353**: 389.

[11] Walls *et al.* (2020) Elicitation of potent neutralising antibody responses by designed protein nanoparticle vaccines for SARS-CoV-2.*Cell*. **183**: 1367.

[12] Arunachalam *et al.* (2021) Adjuvanting a subunit COVID-19 vaccine to induce protective immunity. *Nature.* 594: 253. https://doi.org/10.1038/s41586-021-03530-2

[13] Kuo *et al.* (2020) Development of CpG-adjuvanted stable prefusion SAR-Cov-2 spike antigen as a subunit vaccine against COVD-19. *Nature Scientific reports.* 10: 20085 https://doi.org/10.1038/s41598-020-77077-z.

nonclinical studies supporting the selection of AS03 as the preferred adjuvant for the proposed vaccine. The *in vivo* pharmacology also included studies conducted to support the use of the proposed AS03-adjuvanted vaccine as a booster by comparing the effects of a two-dose versus three-dose regimen. Effects of a bivalent formulation containing RBD-NP-WT and RBD-NP-Beta was also investigated. Studies were also performed against current variants of concern (VOCs).

Recent VOCs include Alpha, Beta, Gamma, Delta and Omicron, which all contain specific mutations within the spike regions.[14] These mutations may lead to evasion of vaccine-induced humoral immunity.[15,16] In addition, neutralising antibody titers induced by vaccination have been found to rapidly reduce over time. To overcome the emergence and spread of these VOCs worldwide, booster immunisations have been implemented worldwide as evidence suggests that a third dose (or booster dose) of vaccine can offer better protection and lessen the development of severe disease than individuals without a booster dose. Studies were therefore undertaken to to demonstrate neutralising capacity and efficacy of anti-RBD antibodies against the wild-type SARS-CoV-2 and VOCs after a two-dose primary immunisation and a booster vaccination with AS03-adjuvanted RBD-NP in a series of immunogenicity studies in BALB/c mice, transgenic mice and NHP (rhesus monkeys).

Studies in Balb/c mice and hACE2 transgenic mice showed that two doses of RBD-NP adjuvanted with AS03 given three weeks apart elicited higher levels of RBD-specific IgG and neutralising antibodies than the Alum-RBD-NP even at the lowest dose of 0.2 µg. Very high titers of anti-RBD IgG and neutralising antibodies were induced after the first vaccine dose with levels rising significantly after the second dose. Similar results were observed when the mice were administered GBP510 adjuvanted with AS03 using the same vaccine schedule. In both Balb/c and transgenic mice, booster or third vaccinations following the primary immunisations resulted in increased titers of antibody levels. Immunisation of Balb/c mice with two doses of AS03-RBD-NP also induced RBD-specific T cells secreting both Th1 cytokine (IFNγ) and Th2 cytokine (IL4), indicating that the AS03-adjuvanted vaccine induced a mixed Th1/Th2 CMI response. Levels of these cytokines were increased following immunisation with a third vaccine dose.

AS03-GBP510 was immunogenic in rat repeat-dose toxicity studies administered two or three doses (each 30 µg) given two weeks apart. High levels of RBD-IgG specific antibody titers were observed after receiving the first dose and levels increased 10-15-fold after the second dose. In the group administered three doses, antibody titers reached a plateau after the second dose and a third immunisation did not increase antibody titers any higher. Levels of igG antibodies were slightly reduced towards the end of the four-week recovery period in all the studies. At all times, higher levels of RBD-IgG antibodies were induced by the AS03-GBP510 compared to 'historical' formulations tested with other adjuvants (Alum+CpG1018, MF59 or Alum alone). Rats in the DART study were immunised repeatedly (up to 5 times) with a lower dose of 12 µg AS03-GBP510 which was also immunogenic inducing very high levels of RBD-IgG antibodies during pregnancy and lactation. Therefore, in rats, both AS03-GBP510 vaccine doses (12 and 30 µg) elicited high antibody titers demonstrating a dose-sparing effect with the use of the AS03 adjuvant.

[14] GISAID (2022). https://www.gisaid.org/hcov19-nts/

[15] Koyama *et al.* (2022) Evasion of vaccine-induced humoral immunity by emerging sub-variants of SARS-CoV-2. *Future Microbiol* **17:**417; Chen *et al.* (2022) Humoral & cellular immune responses of COVID-19 vaccines against SARS-Cov_2 Omicron variant: a systemic review. *Int J Biol Sci.* **18**: 4629.

[16] Dolgin (2021) COVID vaccine immunity is waning – how much does that matter? *Nature.* **597**: 606.

Primary and booster immunisations with 25 µg AS03-GBP510/RBD-NP (0.5 mL) administered either as two-doses given three weeks apart (GBP510; cynomolgus) or three-doses given four weeks apart (RBD-NP, rhesus) in NHP induced high levels of both anti-RBD IgG binding antibodies and neutralising antibodies peaking after the second vaccine dose. Antibody titers started decreasing prior to the third vaccine dose in sera of rhesus monkeys given the three-dose regimen but increased significantly after administration of the third/booster dose. Irrespective of the vaccine regimen (two vs three doses) or schedule (three or four weeks between doses) seroconversion rates were 100% in each group of monkeys (4 per group). As was observed with the mouse studies, peripheral blood lymphocytes from cynomolgus monkeys immunised with AS03-GBP510 induced cytokine profile (IFNγ and IL4) suggestive of a mixed Th1/Th2 CMI response following the two-dose regimen. Levels of cytokines increased following immunisation of the monkeys with a third vaccine dose.

Neutralisation of variants of concern

Neutralising activity of anti-RBD antibodies in sera from AS03-RBD-NP/AS03-GBP510 immunised animals against current VOCs was demonstrated using both live virus and pseudovirus neutralisation assays. High levels of neutralising antibodies were detected against wild-type virus, Beta, Gamma and Omicron variants in sera of Balb/c mice immunised with AS03-RBD-NP given the two-dose and the three-dose regimen administered three weeks apart. Titers against the Beta and Gamma variants were similar to that observed for the wild-type and lower against the Delta and Omicron. Similarly, in hACE2 transgenic mice immunised with AS03-GBP510 using the two-dose regimen given three weeks apart, the neutralising antibodies possessed capacity to neutralise Alpha, Beta, Gamma but less effectively when compared to the wild-type strain. Following a third dose with the nonclinical AS03-RBD-NP, both regimens elicited neutraliing antibodies in transgenic mice also against Alpha, Beta, Gamma and Delta with the highest levels induced following the third-dose regimen.

Immunisation of nonhuman primates (cynomolgus and rhesus monkeys) with 25 µg (proposed clinical dose) of either AS03-GBP510 or AS03-RBD-NP also induced cross-reactive neutralising antibodies against the variants. AS03-GBP510 induced high levels of neutralising antibodies against Alpha, Beta, Delta and Gamma variants in cynomolgus monkeys following immunisation with two doses given three weeks apart, but at much lower levels compared to those against the wild-type SARS-CoV-2 virus as observed in the rodent studies. Similarly, in studies conducted in rhesus monkeys to compare the effects of a two-dose versus a three-dose regimen given four weeks apart, neutralising antibodies against Beta, Delta and Omicron were observed with both regimens. Titers against the variants were lower than that observed for wild-type virus after two doses of AS03-RBD-NP but the activity increased slightly following the third vaccine dose although not at the same level as seen against the wild-type. The data suggest that the proposed SKYCovione® vaccine as booster vaccine may have the potential to offer cross-protection against SAR-CoV-2 variants.

Challenge studies

Evidence for protective efficacy of SKYCovione® vaccine against SARS-CoV-2 infection was provided from challenge studies conducted in hACE2 transgenic mice and NHP models (cynomolgus and rhesus monkeys). These studies were all conducted in animal biosafety level 3 laboratories. These animals were selected as relevant species to assess the vaccine efficacy based on published studies. This is acceptable as they show immunological responses to the SKYCovione ® vaccine. hACE2 transgenic mice expressing human ACE2 can be infected with SARS-CoV-2 virus, with increased viral load in lung tissues similar to that seen in patients with COVID-19, justifying the use of these animals. Cynomolgus and rhesus monkeys

have been shown to be permissive to infection with SARS-CoV-2 which replicates in the upper and lower respiratory tract and causes pulmonary lesions, without any clinical signs, resembling the mild clinical cases of COVID-19 in humans.[17] Like humans, NHP ACE2 receptors have high binding affinity for the SARS-CoV-2 spike protein. The potential of ADE of viral infection was also addressed in these studies.

Prior to viral challenge, the hACE2 transgenic mice were immunised with two vaccine doses of AS03-adjuvanted RBD-NP or GBP510 given three weeks apart in separate studies. Three to four weeks after the last vaccine dose was administered, the mice given AS03-RBD-NP were challenged with wild-type SARS-CoV-2 and those immunised with AS03-GBP510 were challenged with wild-type, Alpha or Beta variants. Immunisation with AS03-RBD-NP or with AS03-GBP510 resulted in 100% survival against challenge with wild-type SARS-CoV-2 virus, Alpha and Beta variants with no significant changes in body weight and temperature. The third booster dose with AS03-RBD-NP also protected transgenic mice against the four variants to the same degree as the two-dose regimen. Lower viral loads in lung tissues of all groups challenged with wild-type or variants were observed in AS03-RBD-NP immunised mice *cf.* unvaccinated animals. Viral loads and histopathology of lung tissues were not performed in transgenic mice immunised with AS03-GBP510 and challenged with the variants type. No evidence of ADE was observed.

Cynomolgus monkeys were immunised with two doses of 25 µg AS03-GBP510 given three weeks apart and challenged with wild-type SARS-CoV-2 28 days after the last vaccine dose. The monkeys were sacrificed seven days after viral challenge. Viral load in both nose and throat swabs were lower and rapidly reduced in the immunised NHPs compared to unvaccinated animals. Rhesus monkeys were immunised twice or three times with 25 µg AS03-RBD-NP given four weeks apart. These animals were challenged 77 days after the first vaccine dose with the Delta variant of SARS-CoV-2 and sacrificed seven days post-infection. Viral replication in nasal swabs and bronchoalveolar lavage fluid was reduced in all vaccinated monkeys with viral clearance occurring faster in animals given the three-dose regimen *cf.* two-dose group. The data generated in the NHP studies showed that 25 µg AS03-RBD-NP/GBP510 vaccine was efficacious not only against the wild-type virus but also against the Delta variant.

One of the limitations of the challenge studies was the relatively short period of evaluation post-challenge with live virus. The post-challenge period in transgenic mice was up to 14 days and 7 days in the cynomolgus and rhesus monkey studies. This evaluation period was appropriate to define the acute disease course in these models of SARS-CoV-2 as published information have shown that animals typically recover from the virus within approximately 14 days after infection. A critical endpoint of these studies was to assess the potential for ADE based on histopathology of which there was no evidence.

Conclusion

In summary, administration of the vaccine adjuvanted with AS03 to different animal models (mouse, rat and NHP) was safe and immunogenic when administered as two or three-dose regimen at doses ranging fronm 0.2-30 µg. The booster dose studies confirmed that the third dose of the vaccine following the primary two doses induced higher immune responses *cf.* animals not given the third dose. Data from cytokine production assays demonstrated that the proposed vaccine formulation induced a Th1/Th2 mixed response. AS03 adjuvanted vaccine was able to prevent or reduce the development of mild COVID-19 clinical signs in the animals challenged with either wild-type SARS-CoV-2 or VOCs, including Omicron.

[17] Salguero *et al.* (2020) Comparison of rhesus and cynomolgus macaques as an authentic model for COVD-19. doi: https://doi.org/10.1101/2020.09.17.301093

The booster or third dose showed better cross-protection against the VOCs. Therefore, the strong responses observed with the GBP510 adjuvanted with AS03 supports its selection as the final vaccine formulation for clinical use.

Safety pharmacology

Safety pharmacology studies are not normally required for vaccine development.[18] However, a series of dedicated GLP-compliant safety pharmacology studies were conducted to evaluate vaccine effects after a single IM dose on the central nervous and respiratory systems in male SD rats and cardiovascular system in male beagle dogs. These studies were conducted with nonclinical batches of GBP510 adjuvanted with either MF59 (GBP510-001B), Alum (GBP510-002), or AS03 (GBP510-001A).

There were no treatment-related effects on the CNS in rats nor on the cardiovascular system in dogs. Three of the formulations: GBP510-001B (MF59-adjuvanted), GBP510-003C (Alum+CpG1018-adjuvanted) and GBP510-001A (AS03-adjuvanted) resulted in an increase of ~2 C in body temperatures as well as eliciting effects on the respiratory system of rats. The administration of GBP510-001A (AS03-adjuvanted) resulted in slight decreases in respiratory rates and increases in both tidal and minute volumes following a single IM administration of either a low (12 µg) or high dose (30 µg) but these effects resolved within 48 hours. Effects on body temperature and respiratory systems of the rat resolved within 48 hours. In addition, treatment-related effects on the respiratory system were reported at doses of 12 and 30 µg of the AS03-adjuvanted GPB510 (the proposed vaccine candidate) given to the rats (assuming a rat weight of 0.2 kg) which are 143-357 times the clinical dose (25 µg) based on mg/kg (assuming human weight of 60 kg). In conclusion, the nonclinical safety data suggest the proposed vaccine product will not have an adverse effect on the respiratory, central nervous and cardiovascular systems in clinical trials.

3.2.2 Pharmacokinetics

No pharmacokinetic studies were conducted with GBP510-AS03 as these are not required for vaccines. This is acceptable and in accordance with the WHO guidelines on nonclinical evaluation of vaccines[19] and ICH S6.[20] Distribution studies are not generally needed for vaccines. The AS03 adjuvant is not novel and has been in clinical use for many years. The intended clinical route of administration is the IM route commonly used for vaccines. The lack of pharmacokinetic drug interactions and other pharmacokinetic studies is acceptable.

3.2.3 Toxicology

Acute toxicity

No single-dose toxicity studies were performed. This is acceptable, with relevant information on acute toxicity available from repeat-dose toxicity studies instead. No acute toxic effects were apparent in rats up to the highest doses tested (30 µg IM).

[18] ICH S7A Safety pharmacology studies for human pharmaceuticals. (November 2000). WHO guidelines on nonclinical evaluation of vaccine adjuvants & adjuvanted vaccines (2013).
[19] WHO Guidelines on Nonclinical Evaluation of Vaccines (2005); Guidelines on the Nonclinical Evaluation of Vaccine Adjuvants and Adjuvanted Vaccines (2014).
[20] ICH guideline S6 (R1) Preclinical safety evaluation of biotechnology-derived pharmaceuticals.

Repeat-dose toxicity

Four repeat-dose pivotal GLP-compliant toxicity studies of two or four weeks' duration were conducted with AS03-GBP510 and 'historical' formulations Alum+CpG1018-GBP510, MF59-GBP510 and Alum-GBP510, followed by four-week recovery periods. The designs of the toxicity studies were in accordance with guidelines in that the proposed vaccine GBP510 was immunogenic in the rat and the extent of measured parameters was adequate. The duration of the pivotal rat study, group sizes and use of both sexes were consistent with ICH guidelines (ICH S9 and ICH M3(R2).The clinical route (IM) was used in all studies and this was considered acceptable. The studies used the highest human dose originally proposed for clinical trials (30 µg GBP510) and animals were given two or three doses at fortnighly intervals (D1, D15 and D1, D15 and D29).

All four vaccine formulations were well tolerated in SD rats. No marked differences were noted in the toxicity profiles of the animals in the four repeat-dose studies. Increases in body temperature were observed in rats administered AS03-GBP510 24 hours after injection. There were no deaths or treatment-related effects on clinical observations, body weight, food consumption, or ocular changes. Non-adverse changes observed in rats in hematology, coagulation and clinical chemistry parameters were indicative of a transient acute phase response or inflammation, which trended towards recovery. Organ weight changes observed in spleen and thymus correlated with extramedullary hematopoiesis associated with cellular immune responses of the vaccine, considered adaptive reversible responses and of no toxicological relevance. These changes had recovered at the end of the 4-week recovery period. There were no systemic findings in any of the animals of both studies

Primary target organs identified in vaccinated rats in the four studies were confined to injection site femoral muscles and gastrocnemius muscle with all four vaccine formulations (AS03-GBP510, Alum+CpG1018-GBP510, MF59-GBP510 and Alum-GBP510) and the liver with the Alum+CpG1018-GBP510 vaccine. Granulomatous inflammation, myofiber necrosis and myofiber atrophy in the injection site and muscles of the hindlimbs are considered to be due to the presence of the adjuvants in the vaccine formulations. Granulomatous inflammation is known as an immunological reaction involving cells of the monocyte/macrophage series. The adjuvants used have been known to induce necrosis and focal inflammation as well as injection site pain due to local tissue damage. These findings in the injections sites were trending towards recovery (Alum-CpG1018-GBP510 and Alum-GBP510) or fully recovered (AS03-GBP510 and MF59-GBP510) at the end of the recovery period.

Under the conditions of the studies, the no observed adverse effect level (NOAEL) of AS03-GBP510 for general toxicity in rats was considered to be 30 µg when administered IM. Each dose of AS03-GBP510 (30 µg) administered via the clinical route is 357-times the proposed full clinical dose of 25 µg on a mg/kg basis, assuming a rat weight of 0.2 kg and human weight of 60 kg, thus providing an acceptable safety margin.

Genotoxicity and Carcinogenicity

No genotoxicity or carcinogenicity studies were conducted in relation to the use of SKYCovione™. This is acceptable based on its duration of use, and the applicable guidelines. The adjuvanted vaccine is used in other vaccines.

Reproductive toxicity

As SKYCovione™ is proposed to be used for the active immunisation of individuals from the age of 18 years, there is potential for administration of the vaccine to pregnant women. A GLP compliant, developmental and reproductive toxicity (DART) study was conducted in SD rats which examined the potential adverse effects of the proposed clinical vaccine (12 µg AS03-GBP510) and a 'historical' vaccine formulation (30 µg Alum-GBP510) or non-adjuvanted GBP510 (30 µg) in pregnant/lactating dams. Female animals were immunised IM twice two weeks apart before mating in order to ensure peak immune responses during the critical phases of pregnancy (e.g., organogenesis). Two vaccine booster doses of each formulation were then administered during gestation on GD8 & GD15 (embryo-fetal period) to evaluate potential direct embryotoxic effects of the components of the vaccine formulation and to maintain an immune response throughout the remainder of gestation. This covers the period from implantation until closure of the hard palate and end of gestation defined as stages C, D and E in the ICH S5A document[21]. Half the dams underwent caesarean section for fetal examination (external, visceral, skeletal) on GD21 and the rest were allowed to give birth naturally and followed through to the end of lactation (LD21). Dams in the latter group were given a third dose during lactation on postnatal day 7 (LD7).

The study was adequately conducted in terms of numbers (50 female rats per treatment group) with 25 females/groups submitted to caesarean sectioning at the end of the gestation and 25 females/group allowed to litter and raise pups until weaning prior to sacrifice and examination. The study complied with FDA Guidance for industry and WHO vaccine guidelines. No male fertility studies were undertaken given there were no adverse effects in male reproductive organs observed in the GLP-complaint repeat-dose toxicity studies.

The vaccine formulations including AS03-GBP510 showed no adverse effects on maternal toxicity, female fertility, embryo-fetal development or pre/post-natal development of the offspring when given 4-5 injections of the test materials. No fetal teratogenic toxicity was observed. The only treatment-related effects were edema and induration at injection sites and enlargement of LNs draining injection sites in dams immunised IM with AS03-adjuvanted and Alum-adjuvanted GBP510, which was not unexpected.

The dose of the AS03-GBP510 induced an active immune response to the vaccine in all dams from the vaccine group. The exposure of fetuses and pups to vaccine-specific maternal antibodies was demonstrated during gestation and postnatal phases. High IgG binding antibody responses were observed in both the dams and pups at parturition (GD 20) and on lactation day 21 indicating strong transfer of antibodies from mother to pups during gestation and after birth during the lactation period. The anti-RBD IgG GMTs remained were 3.5-2.5-fold higher in AS03-adjuvanted animals *cf.* Alum-adjuvanted GBP510. The levels of anti-RBD IgG antibodies in the fetuses were 45, 36 and 20% of levels detected in the corresponding dams vaccinated with non-adjuvanted, Alum-adjuvanted and AS03-adjuvanted vaccines, respectively, showing that all three formulations resulted in the transfer of IgG to the developing fetuses *in utero.* Anti-RBD IgG titers measured in pups were much higher than levels measured in matched dams, confirming the transfer of maternal antibodies in postnatal stages of development via lactation and intestinal uptake. The transfer of the vaccines to fetus and breast milk was not investigated.

[21] ICH-S5A Detection of Toxicity to Reproduction for Medicinal Products

The NOAEL of AS03-GBP510 administration for general toxicity of pregnant rats, embryofetal development, survival, growth and development of F1 animals was considered to be 12 µg when administered IM under the conditions of both studies. Each dose of AS03-GBP510 (12 µg) administered via the clinical route was 48% of the proposed full clinical dose of 25 µg. Assuming a rat weight of 0.2 kg, 12 µg was 143 times the clinical dose (25 µg) based on mg/kg (assuming human weight of 60 kg) providing an acceptable safety margin.

Local tolerance

No dedicated local tolerance studies were conducted, since local tolerance was evaluated during the repeat-dose toxicity studies. This is in line with relevant guidelines. Intramuscular administration induced mild or moderate inflammatory reactions which were not unexpected. Evidence of muscle necrosis, haemorrhage and inflammatory cell infiltrates were observed post IM dosing that persisted in some animals until the end of the study recovery phase. These inflammatory reactions are considered typical of those observed with adjuvanted vaccines and can be interpreted as relatively normal adaptive/repair processes that are associated with tissue injuries associated with IM injections and possibly immunological reactions.

Paediatric use

SKYCovione® vaccine is not proposed for pediatric use and no specific studies in juvenile animals were submitted.

3.2.4 Nonclinical Safety Specification of the Risk Management Plan

Key safety concerns arising from nonclinical data are adequately identified in the Safety Specification of the Risk Management Plan (Part II, Module SII).

3.2.5 Nonclinical conclusions and recommendations

- The nonclinical data package consisted of adequate nonclinical (pharmacology and toxicology) studies conducted with the proposed subunit adjuvanted vaccine, SKYCovione®™ (GBP510-AS03). All pivotal repeat dose and reproductive toxicity studies were GLP-compliant. In general, the composition of the nonclinical dossier submitted met regulatory guidelines for vaccines/adjuvants.

- Immunogenicity studies indicate that SKYCovione®™ is immunogenic. It elicited high antibody titers (anti-RBD IgG and neutralising antibodies) and a cellular immune response skewed towards a mixed Th1/Th2 response in animal models. The studies also assessed the vaccine formulated with different adjuvants. All the adjuvants were demonstrated to be immune enhancers. The data support the proposed use of GBP510 adjuvanted with AS03 for clinical trials.

- Immunisation of animals, including nonhuman primates, with AS03-RBD-NP or AS03-GBP510 vaccine candidates administered either as two- or three-dose regimens given 3 or 4 weeks apart elicited cross-reactive neutralising antibodies against recent SARS-CoV-2 variants (Alpha, Beta, Gamma, Delta and Omicron), although the titers against the variants were in general lower when compared to titers against the original viral strain. This suggests that the vaccine candidate as booster vaccine may have the potential to offer cross-protection against SAR-CoV-2 variants.

- Challenge studies in hACE2 transgenic mice and nonhuman primates (cynomolgus and rhesus monkeys) demonstrated that the AS03-adjuvanted GBP510 induced a significant immune response and provided effective protection in animals challenged not only with wild-type SARS-CoV-2 virus but also with variants of concern (Alpha, Beta, and Delta). The studies confirm that SKYCovione® is effective in reducing viral load and and lung pathology in these animal models with viral clearance occurring faster in animals given three-dose (booster) regimen. No evidence of ADE was observed in any of the animal models.

- Dedicated safety pharmacology studies in rats revealed transient treatment-related increases in body temperature and tidal and minute volumes in respiratory system at doses of 12 and 30 µg of the AS03- GPB510 (the proposed vaccine candidate). Given that these doses are 143-357 times the clinical dose (25 µg) on a mg/kg basis and the transient nature of the effects, the toxicity potential to humans is low.

- Pivotal toxicity studies in SD rats did not identify any concerns. SKYCovione ® was generally well tolerated and induced high levels of specific antibodies. Findings were consistent with immune stimulation and inflammatory responses at injection sites, known to be associated with the intramuscular administration of a vaccine. There are no safety concerns for the use of AS03 adjuvant in SKYCovione ®. Results suggests the toxicity potential to humans is low.

- Reproductive and developmental toxicity study in female SD rats administered four (Caesarean sectioning subgroup) or five (natural birth subgroup) intramuscular doses of 12 µg AS03-GBP510 revealed that SKYCovione® is not teratogenic, embryotoxic or fetotoxic. Although the dose is lower than the proposed clinical dose of 25 µg, the rat dose does exceed the clinical dose by 143-fold on a mg/kg basis. Fetuses and pups were exposed to vaccine-specific maternal antibodies. No data are available of SKYCovione® vaccine placental transfer or excretion in breast milk. Administration of SKYCovione ® in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and fetus.

- In general, no nonclinical issues were identified. The data from the nonclinical studies demonstrate that the GBP510 adjuvanted with AS03 (SKYCovione ®) is safe and well tolerated. There are no nonclinical objections for Emergency Use Listing.

3.3 Clinical overview

3.3.1 Clinical development Programme

Study No./Clinical Phase/Rationale	Study Objectives	Study Population/Planned Number of Subjects	Treatment Regimen	Status
GBP510_003 Phase III* Pivotal study	**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/non-inferior 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	**Cohort 1 (immunogenicity):** N = 1956 healthy or medically stable adults (aged ≥ 18 years) with no history of SARS-CoV-2 infection or COVID-19 vaccination **Cohort 2 (safety):** N = 2077 healthy or medically stable adults (aged ≥ 18 years) regardless of serostatus	**Cohort 1 (immunogenicity):** Randomised 2:1 to receive 2 IM doses of GBP510 or ChAdOx1-S with a 4-week interval **Cohort 2 (safety):** Randomised 5:1 to receive 2 IM doses of GBP510 or ChAdOx1-S with a 4-week interval	Ongoing Interim CSR dated 24 August 2022 (up to median 2.5 M follow up)
GBP510_002 Phase I/II** Supportive study	**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	**Stage 1:** N = 80 healthy adults aged 19-55 years with no history of SARS-CoV-2 infection or COVID-19 vaccination **Stage 2:** N = 240 healthy adults aged 19-85 years with no history of SARS-CoV-2 infection or COVID-19 vaccination **Stage 3**: a maximum of 100 healthy adults aged 19 to 85 years who had received a primary series of 25 µg GBP510 with AS03	**Stage 1:** 2 IM doses (with 4-week interval) of saline placebo or 10 µg or 25 µg GBP510 with or without AS03 **Stage 2:** 2 IM doses (with 4-week interval) of saline placebo or 10 µg or 25 µg GBP510 adjuvanted with AS03 or 25 µg GBP510 Unadjuvanted **Stage 3**: single booster dose (6 to 12 months post 2-dose) of GBP510 25µg adjuvanted with AS03	Ongoing Primary CSR dated 16 August 2022 (up to 6M follow up data)
GBP510_001 Phase I/II Supportive study	**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	**Stage 1:** N = 60 healthy adults aged 19-55 years with no history of SARS-CoV-2 infection or COVID-19 vaccination **Stage 2:** N = 200 healthy adults aged 19-85 years with no history of SARS-CoV-2 infection or COVID-19 vaccination	**Stages 1 and 2:** 2 IM doses (with 4-week interval) of saline placebo or 10 µg or 25 µg GBP510 adjuvanted with Alum	Ongoing Primary CSR dated 25 February 2022

*Phase III – stage 2 booster study is ongoing
Abbreviations: AS03 = Adjuvant System 03; COVID-19 = Coronavirus disease 2019; CSR = Clinical Study Report; IM = intramuscular; SARS-CoV-2 = severe acute respiratory syndrome coronavirus type 2

The SKYCovione™ clinical development program included the following studies:

1) GBP510_001: A 2-Stage, Phase 1/2, Placebo-controlled, Randomized, Observer-blinded, Dose finding Study to Assess the Safety, Reactogenicity, and Immunogenicity of a SARS-CoV-2 Recombinant Protein Nanoparticle Vaccine (GBP510) adjuvanted with Aluminum hydroxide in Healthy Younger and Older Adults. This study was conducted in 14 study centers in the Republic of Korea and aimed at enrolling 60 healthy adults 19-55 years of age (Stage 1) and 200 healthy adults 19-85 years of age (Stage 2); 328 participants ended up being enrolled, 327 of whom received at least one vaccine dose. All participants had no history of SARS-CoV-2 infection or COVID-19 vaccination. The participants were randomized to receive two IM doses (with 4-week interval) of saline placebo or 10 µg or 25 µg GBP510 adjuvanted with Alum.

2) GBP510_002: A 3-Stage, Phase 1/2, Placebo-controlled, Randomized, Observer-blinded, Dose finding Study to Assess the Safety, Reactogenicity, and Immunogenicity of a SARS-CoV-2 Recombinant Protein Nanoparticle Vaccine (GBP510) adjuvanted with or without AS03 in Healthy Younger and Older Adults. This study was conducted in 14 study centers in the Republic of Korea, aimed at enrolling 80 healthy adults 19-55 years of age (Stage 1), 240 healthy adults 19-85 years of age (Stage 2) – participants of Stages 1 and 2 with no history of SARS-CoV-2 infection or COVID-19 vaccination – and a maximum of 100 adults 19-85 years of age (Stage 3) who had received a primary series of 25 µg GBP510 with AS03. Participants were randomized to two IM doses (with 4-week interval) of saline placebo or 10 µg or 25 µg GBP510 with or without AS03 (Stage 1), and two IM doses (with 4-week interval) of saline placebo or 10 µg or 25 µg GBP510 adjuvanted with AS03 or 25 µg GBP510 unadjuvanted (Stage 2). In Stage 3 participants received a single booster dose (6 to 12 months post 2-dose) of GBP510 25µg adjuvanted with AS03.

3) GBP510_003: A Phase 3, Randomized, Active-controlled, Observer-blind, Parallel group, Multi-center Study to Assess the Immunogenicity and Safety of SK SARS-CoV-2 Recombinant Protein Nanoparticle Vaccine adjuvanted with AS03 (GBP510) in Adults Aged 18 Years and Older. This study was conducted in study centers in the Republic of Korea, Thailand, The Philippines, Vietnam, Ukraine, and New Zealand, and involved a total of 4036 participants (3821 adults aged 18-64 years and 215 adults aged ≥65 years). Cohort 1 (immunogenicity) (n = 1956) included healthy or medically stable adults aged ≥18 years with no history of SARS-CoV-2 infection or COVID-19 vaccination who were randomized 2:1 to receive two IM doses of GBP510 or ChAdOx1-S with a 4-week interval. Cohort 2 (safety) (n = 2080) included healthy or medically stable adults aged ≥18 years regardless of serostatus who were randomized 5:1 to receive two IM doses of GBP510 or ChAdOx1-S with a 4-week interval. Each subject will be followed up for 12 months post second vaccination. The product (GBP510) used in the phase III trial was identical in formulation to the to-be-marketed product.

4) A Stage 2 booster study (Stage 2 of GBp510_003) was initiated in June 2022 in the Republic of Korea, with 450 adults and elderly aged 18 years and older to be proposed (a subset of 300 in test group, 150 in control group from cohort 1 of Stage 1.

3.3.2 Study population

According to the Applicant, all three studies included only healthy participants. Participants with a history of COVID-19 were excluded from the two phase I/II studies and from the immunogenicity cohort in the

phase III study. Subjects with immunodeficiency, autoimmune disease, bleeding disorder contraindicating IM vaccination, hypersensitivity, or severe allergic reaction (e.g., anaphylaxis, Guillain-Barré syndrome) to any vaccines or components of GBP510, or who were pregnant, or breastfeeding were not included in the studies. In addition, subjects with previous vaccination with any COVID-19 vaccine were excluded from all three studies. Individuals with history of severe acute respiratory syndrome (SARS) or Middle East Respiratory Syndrome (MERS) vaccination were also excluded from the phase III study.

3.3.3 Vaccine efficacy

No efficacy trial was conducted with this vaccine. According to the Applicant, the EMA accepted an immunobridging approach to COVID-19 vaccine ChAdOx1-S (Vaxzevria, AstraZeneca AB) for a pivotal phase III study (Scientific Advice 15 June 2021; EMA/SA/0000062495). Therefore, the results of the immunogenicity analyses are provided. SARS-CoV-2-neutralizing antibody response was tested as a surrogate for efficacy, and results were presented along with RBD-binding immunoglobulin G (IgG) antibody responses and cell-mediated immunity (CMI).

3.3.3.1 Immunogenicity

The Applicant claims that immunogenicity assessments of the candidate vaccine were conducted by qualified and certified laboratories. The assays were validated as required in the EMA guideline on clinical evaluation of vaccines (EMEA/CHMP/VWP/164653/05 Rev. 1). Assays used for the determination of the immune response after vaccination (IgG ELISA, PRNT, PBNA, and ICS, for the phase I/II trials, and IgG ELISA, FRNT, Fluorospot, and ICS/FACS for the phase III trial) and their validation reports are presented in Module 2.7.1 of the CTD. In all 3 studies, the immunogenicity samples were tested at central laboratories in South Korea. The plaque-reduction neutralization test (PRNT) was performed at the Zoonosis Research Institute, Jeonbuk National University, and the focus-reduction neutralization test (FRNT) was performed at the Korean National Institute of Health and the International Vaccine Institute. All the other assays were performed at the Sponsor laboratory. Assessment of immunogenicity was a secondary objective in Stage 1 and a primary objective in Stage 2 of both phase I/II studies. Endpoints included:

- Geometric Mean Titer (GMT) of IgG antibody to the SARS-CoV-2 RBD measured by enzyme-linked immunosorbent assay (ELISA)
- Geometric Mean Fold Rise (GMFR) of IgG antibody to the SARS-CoV-2 RBD from baseline measured by ELISA
- SCR from baseline in ELISA IgG titer
- GMT of neutralizing antibody to the SARS-CoV-2 measured by pseudovirus and wild-type virus neutralization assays
- GMFR of neutralizing antibody to the SARS-CoV-2 from baseline measured by pseudovirus and wild-type virus neutralization assays
- SCR from baseline in pseudovirus and wild-type neutralizing antibody titer
- Cell-mediated response for both T helper 1 cell (Th1) and T helper 2 cell (Th2) (e.g., INF-γ, Interleukin-4 [IL-4] using Enzyme-linked ImmunoSpot [ELISpot] or other system)

In the phase III study (GBP510_003), the primary objective was to demonstrate that the immune response induced by 2 doses of GBP510 25µg adjuvanted with AS03 at a 4-week interval in seronegative

adults aged 18 years and older was superior/non-inferior to the immune response induced by 2 doses of ChAdOx1-S.

The primary endpoints were the following:

- For superiority: GMT of neutralizing 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 neutralizing antibody titer from baseline to 2 weeks post 2nd vaccination.

The secondary endpoints (immunogenicity) were:

- GMT, GMFR, and SCR of SARS-CoV-2 RBD-binding IgG antibody measured by ELISA.
- GMT, GMFR, and SCR of neutralizing antibody to the SARS-CoV-2 measured by wild-type virus assays (FRNT)
- Cell-mediated response for both Th1and Th2 cytokines measured by ELISpot and/or FluoroSpot, and for both CD4+ and CD8+ T-cells measured by FACS.

In Study GBP510_001 higher GMTs and GMFRs for IgG and neutralizing antibodies were observed in the GBP510 25 µg adjuvanted with Alum group than in the GBP510 10 µg adjuvanted with Alum group at two and four weeks after Dose 2; SCRs were high in both active groups (> 92% for all three assays at two weeks after Dose 2). Post-vaccination GMTs for immune response induced by GBP510 25 µg adjuvanted with Alum exceeded those in the pooled human convalescent plasma standards in the WHO representative panel for anti-SARS-CoV-2 antibody. In CD4+ cells, both active doses induced cytokine production with a dominant Th1 profile.

In Study GBP510_002, higher GMTs and GMFRs for IgG and neutralizing antibodies were observed in the GBP510 25 µg adjuvanted with AS03 group compared to the 10 µg adjuvanted with AS03 group at two weeks after Dose 2. Seroconversions (SCRs) for all three assays were >99% at two weeks after Dose 2 in adjuvanted groups. The GBP510 25 µg adjuvanted with AS03 group was chosen for evaluation in the pivotal Phase III study. Post-vaccination GMTs for immune response induced by GBP510 25 µg adjuvanted with AS03 substantially exceeded those in the WHO representative panel. In CD4+ cells, both adjuvanted doses induced cytokine production with a dominant Th1 profile.

Study GBP510_003 achieved both co-primary endpoints. At two weeks after Dose 2, the neutralizing antibody GMT following GBP510 25 µg adjuvanted with AS03 was superior to that seen after ChAdOx1-S, as demonstrated by the lower limit of the 95% confidence interval (CI) for the ratio of adjusted GMTs of 2.63. At the same time point, SCR following GBP510 25 µg adjuvanted with AS03 was non-inferior to that following ChAdOx1-S, as demonstrated by the lower limit of the 2-sided 95% CI for the difference of the SCRs of 7.68%.

The immunogenicity data is summarized in the tables below:

Table 2.7.3-8 SARS-CoV-2-neutralising Antibody Results by Wild-Type Virus Neutralisation Assays in Phase I/II Studies of GBP510 (Per-Protocol Set) - Plaque Reduction Neutralisation Test

Time Point	Statistic (95% CI)	Plaque Reduction Neutralisation Test							
		GBP510_001			GBP510_002				
		10 µg GBP510 + alum N =23	25 µg GBP510 + alum N = 24	Placebo N = 15	10 µg GBP510 + AS03 N = 23	10 µg GBP510 N = 4	25 µg GBP510 + AS03 N = 21	25 µg GBP510 N = 9	Placebo N = 19
Baseline	GMT	4.2 [3.4, 5.2]	4.9 [3.8, 6.5]	5.4 [3.9, 7.4]	4.4 [3.5, 5.5]	9.0 [9.0, 9.0]	4.3 [3.4, 5.5]	4.3 [2.8, 6.6]	4.8 [3.6, 6.2]
2 weeks post-Dose 2	GMT	204.5** [138.7, 301.5]	288.4** [174.9, 475.6]	5.4 [3.9, 7.4]	949.8** # [670.4, 1345.8]	34.1 [1.9, 597.4]	861.0** # [649.6, 1141.1]	58.1* [16.6, 203.1]	4.8 [3.6, 6.2]
	GMFR	48.8** [35.0, 68.0]	58.4** [35.1, 97.2]	1.0 [1.0, 1.0]	216.1** # [158.8, 294.0]	3.8 [0.2, 66.4]	199.0** # [151.2, 261.9]	13.4* [4.2, 42.7]	1.0 [1.0, 1.0]
	SCR	100** [85.2, 100]	95.8** [78.9, 99.9]	0.0 [0.0, 21.8]	100** # [85.2, 100]	50.0* [6.8, 93.2]	100** [83.9, 100]	77.8** [40.0, 97.2]	0.0 [0.0, 17.7]
Statistical significance		**$P < 0.0001$ vs placebo			*$P < 0.05$ vs placebo **$P < 0.0001$ vs placebo #$P < 0.05$ vs matching dose without adjuvant				

Sources: GBP510_001 CSR Table 12.1-3, GBP510_002 CSR Table 12.1-3
Abbreviations: CI = confidence interval; GMFR = geometric mean fold rise; GMT = geometric mean titre; N = number of subjects; SCR = seroconversion rate.

Table 2.7.3-9 SARS-CoV-2-neutralising Antibody Results by PBNA in Phase I/II Studies of GBP510 (Per-Protocol Set)

Time Point	Statistic [95% CI]	GBP510_001			GBP510_002				
		10 µg GBP510 + alum N =97	25 µg GBP510 + alum N = 95	Placebo N = 56	10 µg GBP510 + AS03 N = 93	10 µg GBP510 N = 10	25 µg GBP510 + AS03 N = 96	25 µg GBP510 N = 45	Placebo N = 58
Baseline	GMT	18.4 [17.4, 19.5]	19.6 [18.0, 21.4]	19.5 [17.5, 21.8]	18.1 [17.2, 19.0]	21.0 [15.2, 29.1]	19.5 [18.1, 21.0]	19.1 [16.9, 21.4]	19.2 [17.2, 21.4]
4 weeks post-Dose 1	GMT	32.7* [27.1, 39.4]	35.7* [29.0, 44.0]	22.2 [18.8, 26.2]	40.0** [32.5, 49.1]	32.8 [17.3, 62.2]	40.9** [33.3, 50.3]	21.2 [18.3, 24.7]	19.7 [17.5, 22.2]
	GMFR	1.8* [1.5, 2.2]	1.8* [1.5, 2.3]	1.1 [0.9, 1.4]	2.2** [1.8, 2.7]	1.6 [0.8, 2.9]	2.1** [1.7, 2.6]	1.1 [1.0, 1.3]	1.0 [0.9, 1.2]
	SCR	23.7* [15.7, 33.4]	25.3* [16.9, 35.2]	8.9 [3.0, 19.6]	30.1* [21.0, 40.5]	10.0 [0.3, 44.5]	28.1* # [19.4, 38.2]	4.4 [0.5, 15.2]	6.9 [1.9, 16.7]
2 weeks post-Dose 2	GMT	322.4** [253.6, 409.9]	397.8** [312.1, 507.1]	23.7 [19.6, 28.7]	1369.0** # [1124.5. 1666.7]	83.5* [28.6, 243.5]	1431.5** ## [1171.1, 1749.7]	63.9** [44.6, 91.5]	19.2 [17.4, 21.3]
	GMFR	17.5** [13.7, 22.5]	20.3** [15.9, 25.9]	1.2 [1.0, 1.5]	75.8** ## [61.9, 92.9]	4.0* [1.5, 10.9]	73.4** ## [59.3, 91.0]	3.4** [2.3, 4.9]	1.0 [0.9, 1.1]
	SCR	92.8** [85.7, 97.1]	94.7** [88.1, 98.3]	14.3 [6.4, 26.2]	100.0** ## [96.1, 100.0]	50.0* [18.7, 81.3]	99.0** ## [94.3, 100.0]	51.1** [35.8, 66.3]	1.7 [0.0, 9.2]
4 weeks post-Dose 2	GMT	219.5** [174.9, 275.6]	281.1** [224.3, 352.1]	22.1 [19.0, 25.7]	838.8** ## [681.7, 1032.1]	68.5* [26.1, 179.8]	1107.3** ## [911.4, 1345.3]	51.9** [36.1, 74.6]	19.3 [17.4, 21.4]
	GMFR	11.9** [9.4, 15.1]	14.3** [11.4, 18.0]	1.1 [1.0, 1.4]	46.5** ## [37.6, 57.4]	3.3* [1.2, 9.0]	56.8** ## [45.6, 70.7]	2.7** [1.8, 4.0]	1.0 [0.9, 1.2]
	SCR	86.6** [78.2, 92.7]	92.6** [85.4, 97.0]	5.4 [1.1, 14.9]	97.9** ## [92.5, 99.7]	50.0* [18.7, 81.3]	99.0** ## [94.3, 100.0]	42.2** [27.7, 57.9]	3.5 [0.4, 11.9]
Statistical significance		*$P < 0.05$ vs placebo **$P < 0.0001$ vs placebo			*$P < 0.05$ vs placebo **$P < 0.0001$ vs placebo #$P < 0.05$ vs matching dose without adjuvant ##$P < 0.0001$ vs matching dose without adjuvant				

Sources: GBP510_001 CSR Table 12.1-2, GBP510_002 CSR Table 12.1-2
Abbreviations: CI = confidence interval; GMFR = geometric mean fold rise; GMT = geometric mean titre; PNBA = pseudovirus-based neutralisation assay; SCR = seroconversion rate.

Table 2.7.3-5 Neutralising Antibody Response in Participants with SARS-CoV-2 Antibody Level ≥ Lower Limit of Quantification at Screening Visit (Full Analysis Set)- Study GBP510_003

Statistic	25 µg GBP510 + AS03			CHAdOx1-S		
	Baseline	4 weeks post-Dose 1	2 weeks post-Dose 2	Baseline	4 weeks post-Dose 1	2 weeks post-Dose 2
Wild-Type Virus Neutralisation Assays						
n	133	38	127	66	20	64
GMT [95% CI]	39.7 [33.4, 47.2]	329.4 [147.9, 733.6]	989.6 [773.0, 1266.9]	41.8 [33.2, 52.7]	339.8 [162.9, 708.7]	473.6 [338.1, 663.2]
Ratio of GMT [95% CI]	1.0 [0.7, 1.3]	1.0 [0.3, 2.8]	2.1 [1.4, 3.2]	–	–	–
P-value*	0.7282	0.9532	0.0007	–	–	–
GMFR [95% CI]	–	7.1 [3.2, 15.8]	24.2 [18.1, 32.5]	–	7.2 [2.9, 18.0]	11.2 [7.2, 17.2]
Participants with ≥4-fold increase, % [95% CI]	–	57.9 [40.8, 73.7]	89.8 [83.1, 94.4]	–	60.0 [36.1, 80.9]	76.6 [64.3, 86.3]
Enzyme-Linked Immunosorbent Assay						
n	674	674	646	333	333	323
GMT [95% CI]	25.0 [23.8, 26.1]	382.2 [344.8, 423.8]	2908.4 [2732.2, 3096.0]	24.8 [23.3, 26.4]	197.8 [175.7, 222.7]	325.9 [295.0, 360.1]
Ratio of GMT [95% CI]	1.0 [0.9, 1.1]	1.9 [1.7, 2.3]	8.9 [7.9, 10.0]	–	–	–
P-value*	0.8827	<0.0001	<0.0001	–	–	–
GMFR [95% CI]	–	15.3 [14.0, 16.8]	115.8 [106.5, 126.0]	–	8.0 [7.1, 9.0]	13.1 [11.7, 14.6]
Participants with ≥4-fold increase, % [95% CI]	–	88.4 [85.8, 90.7]	98.1 [96.8, 99.0]	–	75.7 [70.7, 80.2]	92.0 [88.4, 94.7]

Source: GBP510_003, Table 14.4.1 and Table 14.4.3
Abbreviations: n = number of participants with available results in a specific time point; GMT = geometric mean titre; CI = confidence interval; GMFR = geometric mean fold rise.
Ratio of GMT is calculated as GBP510 / CHAdOx1-S.
* Testing for difference between treatment groups (two sample *t*-test)
95% CIs for GMT and GMFR are calculated using Wald method with t-distribution.

Table 2.7.3-11 RBD-binding Immunoglobulin G Antibody (ELISA) in Phase III study GBP510_003 (Per-Protocol Set)

Statistic	25 µg GBP510 + AS03			CHAdOx1-S		
	Baseline	4 weeks post-Dose 1	2 weeks post-Dose 2	Baseline	4 weeks post-Dose 1	2 weeks post-Dose 2
n	877	877	877	441	441	441
GMT [95% CI]	10.9 [10.5, 11.3]	171.7 [162.6, 181.4]	3230.4 [3074.9, 3393.7]	10.8 [10.3, 11.3]	119.5 [110.0, 129.8]	248.5 [230.5, 267.8]
Ratio of GMT [95% CI]	1.0 [1.0, 1.1]	1.4 [1.3, 1.6]	13.0 [11.9, 14.2]	–	–	–
P-value*	0.7409	<0.0001	<0.0001	–	–	–
GMFR [95% CI]	–	15.7 [14.8, 16.8]	296.1 [278.1, 315.2]	–	11.1 [10.1, 12.2]	23.0 [21.1, 25.1]
Adjusted GMT[1] [95% CI]	–	131.2 [117.9, 146.1]	2850.5 [2586.5, 3141.3]	–	91.9 [81.6, 103.6]	215.7 [193.5, 240.4]
Ratio of GMTs [95% CI]	–	1.4 [1.3, 1.6]	13.2 [12.1, 14.4]	–	–	–
P-value[1]	–	<0.0001	<0.0001	–	–	–
Adjusted GMT[2] [95% CI]	–	131.2 [114.2, 150.7]	2633.7 [2321.9, 2987.4]	–	91.0 [78.5, 105.5]	198.4 [173.4, 227.1]
Ratio of GMT [95% CI]	–	1.4 [1.3, 1.6]	13.3 [12.2, 14.5]	–	–	–
P-value[2]	–	<0.0001	<0.0001	–	–	–
SCR, % [95% CI]	–	92.5 [90.5, 94.1]	99.5 [98.8, 99.9]	–	84.8 [81.1, 88.0]	96.8 [94.7, 98.3]

Source: GBP510_003, Table 14.2.4

Abbreviations: n = number of participants with available results in a specific time point; GMT = geometric mean titre; CI = confidence interval; GMFR = geometric mean fold rise. SCR = seroconversion rate; Ratio of GMT is calculated as GBP510 / CHAdOx1-S.

*Testing for difference between treatment groups (two sample t-test)

[1] ANCOVA model with treatment group, age group (18 – 64, ≥65) as factors, and baseline antibody level as covariate

[2] ANCOVA model with treatment group, age group (18 – 64, ≥65), sex, race as factors and baseline antibody level as covariate

The 95% CIs for GMTs and GMFRs are calculated using Wald method with t-distribution.

The 95% CI of SCR is calculated based on Clopper-Pearson method.

Cell-mediated Immunity (CMI) was measured by ICS in a subset of subjects in the phase I/II studies and the phase III study. In Study GBP510_001, in CD4+ cells, both active doses induced cytokine production with a dominant Th1 profile. Cells expressing IFN-γ, TNF-α, and IL-2 increased in both active dose groups compared to the placebo group at two weeks post-Dose 2, while the frequency of cells expressing IL-4 was lower in the GBP510 25 µg adjuvanted with Alum group than in the placebo group. In Study GBP510_002, in CD4+ cells, both adjuvanted doses induced cytokine production with a dominant Th1 profile. IFN-γ and IL-2 increased notably in the adjuvanted dose groups compared to the unadjuvanted dose groups. Cells expressing IFN-γ and IL-2 increased notably in both adjuvanted dose groups compared to the placebo group at two weeks post-Dose 2, while the frequency of cells expressing IL-4 was lower in the adjuvanted dose groups than in the placebo group. IL-5 was rarely detected in any of the groups.
There was no clear pattern of cytokine production seen in CD8+ cells. In Study GBP510_003, in CD4+ and CD8+ T cells, GBP510 induced cytokine production with a higher Th1 profile as compared to ChAdOx1-S. IL-2 increased notably in the GBP510. group compared to the ChAdOx1-S at 2-weeks post-Dose 2. The number of samples tested was low, and significant difference was only seen in the expression of CD4+ T-cells expressing IL-2 at 2-weeks post-Dose 2; however, cells expressing IFN-γ increased slightly in GBP510 dose group compared to the ChAdOx1-S at 2 weeks post-Dose 2 (p-value = 0.0184). There was no change observed in the expression of IL-4 for either dose group.

For all three clinical trials, long-term follow-up is ongoing through 12 months after Dose 2. In the phase II study GBP510_002, the subjects in the 25 µg GBP510 with AS03 dose group showed persistent antibody response 6 to 12 months after the primary series (mean booster interval was approximately 7.5 months).

3.3.4 Subgroup analysis of efficacy

3.3.4.1 Vaccine Safety

In the phase III study (GBP510_003) assessment of safety was a secondary objective with endpoints including adverse events (AEs) (solicited and unsolicited AEs, adverse events of special interest [AESI], medically attended adverse events [MAAEs], serious AEs [SAEs], deaths and medically attended adverse drug reactions [MAADRs]). For the phase I/II studies (GBP510_001 and GBP510_002), in Stage 1 of both

studies, safety and reactogenicity were the primary objective with endpoints including AEs (solicited and unsolicited) AESIs, MAAEs, SAEs, deaths, MAADRs, vital signs, electrocardiogram (ECG), physical examination, and clinical safety laboratory parameters. These measures (excluding vital signs, ECG, physical examination and clinical safety laboratory parameters) were a secondary objective in Stage 2 of both studies.

The safety database of individuals who received at least one dose of the GBP510 25 µg adjuvanted with AS03 vaccine candidate has currently 3133 subjects (n = 104 participants in Study GBP510_002 and n = 3029 participants in Study GBP510_003).

The most reported AEs within 4 weeks after primary vaccination were injection site pain (55.7%), fatigue (31.1%), myalgia (30.5%), and headache (29.9%). Most of these AEs were mild to moderate in severity and resolved within a few days after vaccination. Overall, the frequency of adverse events was higher in the younger adult group (18 to 64 years) than in the elderly group (65 and over) and the frequency of AEs after the first dose was higher than after the second dose. They were reported more often in Korean and Caucasian than in Southeast Asian clinical trial participants.

Adverse events observed during clinical trials by frequency categories were the following:

- Very Common (≥1/10): headache, arthralgia, myalgia, injection site pain, fatigue, chills, fever
- Common (≥1/100 to <1/10): nausea/vomiting, diarrhea, injection site redness, injection site swelling
- Uncommon (≥1/1000 to <1/100): dizziness, paresthesia, pain in extremity, injection site pruritus, injection site warmth, pain, chest pain, rash, oropharyngeal pain, cough, palpitations
- Rare (≥1/10 000 to < 1/1000): lymphadenopathy, hypoesthesia, abdominal pain, dyspepsia, back pain, groin pain, asthenia, pruritus, hyperhidrosis, decreased appetite, upper respiratory tract infection, melanocytic naevus.

No adverse event of special interest (AESI) was reported in studies GBP510_001 and GBP510_002. In Study GBP510_003, after a median of 2.5 months follow up, there were 3 (0.07%) AESIs reported: ‘acute kidney injury’, ‘glomerulonephritis rapidly progressive’, and ‘pancreatitis acute’. AESIs were not related to the IPs except for the 'Glomerulonephritis rapidly progressive' case. The incidence of AESIs was evenly distributed across treatment groups. In the control group, two single AESIs of ‘anaphylactic reaction’ and ‘psoriasis’ have been reported.

Two SAEs were reported in Study GBP510_001, ‘skin laceration’ in the GBP510 25 µg adjuvanted with Alum group, and ‘calculus urinary’ in the placebo group. In Study GBP510_002, there were 3 SAEs reported: ‘hemorrhoids’ in 1 participant in the GBP510 25 µg adjuvanted with AS03 group, breast cancer and road traffic accident in 1 participant each in the GBP510 25 µg group. A total of 24 SAEs were reported in Study GBP510_003, nine of them serious COVID-19 cases. SAEs included one case each of ‘appendicitis’, ‘hand fracture’, ‘pneumonia’, ‘rotator cuff syndrome’, ‘anal abscess’, ‘skin laceration’, ‘schizophrenia’, ‘glomerulonephritis rapidly progressive’, ‘cholecystitis acute’, ‘cholangitis acute’, ‘cardiopulmonary failure’, ‘acute myocardial infarction’, ‘pancreatitis acute’ and two of ‘gastroesophageal reflux disease’. The case of rapidly progressive glomerulonephritis is mentioned in the proposed product insert as a serious adverse drug reaction. Except for this case all the other SAEs were considered as not related to the candidate vaccine. All SAEs reported in Study GBP510_001, GBP510_002 and GBP510_003 were confirmed within 4 weeks after the dose 2.

In Study GBP510_003, after a median of 2.5 months follow up, one death due to brain neoplasm was reported in the treatment group. One death due to cardio-respiratory failure was reported in the control group. Both cases were assessed to be not related to the study (candidate and comparator) vaccines. No deaths occurred in studies GBP510_001 and GBP510_002.

3.3.5 Subgroup analysis of safety

Pregnancy

Pregnant women were excluded from the studies. However, there were six pregnancy reports were collected during the reporting period of the interim CSR of the GBP510_003 study. There are no pregnancy reports with abnormal outcome or serious adverse event, none withdrew from the study, and all are kept under monitoring until delivery. Further information will be required in this important population

3.3.6 Neutralization against SARS-CoV -2 Variants of Concern

In Study GBP510_003, which compared 25 µg GBP510 with AS03 and ChAdOx1-S, GMTs were similar at baseline in the 2 groups. The study achieved both co-primary endpoints at 2 weeks post-Dose 2. Neutralising antibody GMT of 25 µg GBP510 with AS03 was superior to that of ChAdOx1-S, and SCR (percentage of subjects with ≥ 4-fold rise from baseline) of 25 µg GBP510 with AS03 was non-inferior to that of ChAdOx1-S. GBP510 with AS03 elicited a significantly (P<0.0001) greater immune response against both Delta (strain tested: GK clade; AY.69 lineage) and Omicron (strain tested: GRA clade; B.1.1.529 lineage) variants by the second week after Dose 2 than did ChAdOx1-S. The ratio of GMTs (GBP510 / ChAdOx1-S) observed for Delta and Omicron variants was 27.27 and 10.52, respectively.

Immunogenicity Assessment by Live Virus Neuralisation Assays (FRNT50) Against the Delta and Omicron Variant – Exploratory Endpoint Analysis (Per-Protocol Set)- Study GBP510_003

Time Point	Statistic	25 µg GBP510 + AS03 N = 877	CHAdOx1-S 5 × 10^{10} vp N = 441	P-value[a]
2 weeks post-Dose 2	**Delta Variant**			
	n	137	68	–
	GMT [95% CI]	2644.3 [2269.5, 3080.8]	97.0 [69.3, 135.7]	–
	Ratio of GMTs [95% CI] [GBP510 / CHAdOx1-S]	27.3 [18.9, 39.4]	–	< 0.0001
2 weeks post-Dose 2	**Omicron Variant**			
	n	137	68	–
	GMT [95% CI]	129.1 [107.4, 155.2]	12.3 [10.3, 14.6]	–
	Ratio of GMTs [95% CI] [GBP510 / CHAdOx1-S]	10.5 [8.2, 13.5]	–	< 0.0001

Sources: GBP510_003 Table 14.4.5 and GBP510_003 Table 14.4.7
Abbreviations: CI = confidence interval; GMT = geometric mean titre; SD = standard deviation; vp = viral particles.

3.4 Risk Management Plan

The risk management assessment was based on the RMP version 1.0 SARS-CoV-2 (Covid-19) Vaccine [SKYCovione]

a. Important identified risks:

SKYCovione	WHO	Comments
---	Anaphylaxis	Anaphylaxis is known to be possible with any injectable vaccine. Anaphylaxis can be upgraded to an identified risk based on the outcome of the assessment of the clinical data of ongoing studies or post-marketing information. A minimum period of 15-minutes of observation is recommended for each vaccinee after vaccination, given the risk of potentially life-threatening anaphylactic/anaphylactoid reactions

b. Important potential risks:

SKYCovione	WHO	Comments
Vaccine-associated enhanced disease (VAED)	Vaccine-associated enhanced disease (VAED)	There is a theoretical concern that vaccination against SARS-CoV-2 may be associated with enhanced severity of COVID-19 episodes which would manifest as VAED. The adverse events following immunization (AEFIs) along with VAED for SKYCovione are monitored by active surveillance through Sentinel sites and also through Ministry of Health and Family Welfare (MOHFW) safety database (AEFI cases approved by National AEFI Committee) and also through stimulatory information from Sale staff and through Medical Information Call Center (MICC), BioE website (PV mail id), social media (Twitter, FB, Linkedin) Although, VAED has not been reported for any of the COVID-19 vaccines including SKYCovione, the theoretical risk is higher with inactivated vaccines than the protein subunit vaccines, because they contain proteins that are not involved in neutralization. Inactivated COVID-19 vaccines include incomplete inactivation of viral particles causing the vaccine to retain virulence and cause disease, and development of vaccine associated enhanced disease (VAED) when vaccinated individuals encounter the pathogen after being vaccinated.
	Programmatic errors	It may be necessary to minimize this situation in advance under real use conditions. It will be monitored via routine pharmacovigilance activities and will be presented in each PBRER/PSUR
Potential Immune Mediated Disorder (pIMDs)	Potential Immune Mediated Disorder (pIMDs)	As limited pIMDs cases have been reported from clinical trials and the safety of GBP510 adjuvanted with AS03 has not been evaluated in real world setting, routine Pharmacovigilance (PV) activities and additional PV activities be conducted to obtain data to further characterize of cases of pIMD.

c. Missing information:

SKYCovione™	WHO	Comments
Use in pregnancy and while breastfeeding	Use during pregnancy and while breastfeeding	There is a limited experience with use of GBP510 adjuvanted with AS03 in pregnant or lactating women, or from women who became pregnant after vaccinated with GBP510 adjuvanted with AS03. While non-clinical studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/fetal development, parturition, or post-natal development, the effect of GBP510 adjuvanted with AS03 on the foetus and breastfed infant is unknown, as data are currently insufficient to assess the risk. As GBP510 adjuvanted with AS03 is intended for use in a large population, the collection of pregnancy and infant outcomes data is necessary to characterize the safety profile in this population. Although 8 cases of pregnancy were reported during clinical trials of GBP510 adjuvanted with AS03, no safety concerns relevant to pregnancy was raised. Use of GBP510 adjuvanted with AS03 will be investigated in the planned database study as the additional PV activity. In the mRNA COIVD-19 vaccines in pregnancy investigated the infection rate, maternal antibody response, transplacental antibody transfer, and adverse events, it was confirmed that safety profile has no difference compared to general population (Pratama, 2022).
	Use in pediatric population <18 years of age	Paediatric patients younger than 18 years is considered missing information.
Use in immunocompromised subjects	Use in immunocompromised patients, including HIV	The vaccine has not been studied in individuals with immunocompromising conditions in clinical trials. Routine and additional PV activities will be conducted to characterize safety profile of immunocompromised subjects administered with GBP510 adjuvanted with AS03
	Use in patients with autoimmune or inflammatory disorders	The safety data in patients with autoimmune or inflammatory disorders is limited. The applicant should consider evaluating safety and immunogenicity of SKYCovione in patients with autoimmune or inflammatory disorders. The applicant needs to provide details on how the safety information from this population will be collected.
Use in frail subjects with comorbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders, autoimmune or inflammatory disorders)	Use in frail subjects with co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)	The safety data in frail individuals with comorbidities is limited. The vaccine has not been studied in individuals with severe comorbidities that may compromise immune function due to the condition or treatment of the condition. Patients with comorbidities (e.g., COPD, DM, chronic neurological disease, cardiovascular disorders, autoimmune or inflammatory disorders) are potentially at risk of developing a more severe manifestation of COVID-19. Although, there is no evidence that the safety profile in this population receiving GBP510 adjuvanted with AS03 will be different to that of the general population, but given the scarcity of data, the possibility cannot be excluded.

Interaction with other vaccines	Interaction with other vaccines	The safety, immunogenicity, and efficacy of this vaccine when co-administered with other vaccines (e.g. influenza) has not been evaluated. There is limited information on the safety of the vaccine when administered with other vaccines as the safety of GBP510 adjuvanted with AS03 when co-administered with other vaccines has not been evaluated in ongoing clinical trials. Therefore, given the paucity of the data, the possibility that the safety profile of the subjects receiving GBP510 adjuvanted with AS03 when co-administered with other vaccines would be different from those of the general population cannot be excluded Therefore, the potential impact on safety and efficacy of SKYCovione is unknown. Interaction with other vaccines needs to be studied in post-marketing.
	Interchangeability or sequential use with other vaccines	The evidence to support interchangeability or sequential use with other COVID-19 vaccines is limited. In the absence of a customized trial to this effect, it is not advisable to interchange the vaccines in primary immunization schedule as the currently available vaccines belong to different technology platforms. However, such a sequential activity would be considered once the long-term persistence and booster data is available. As a step forward towards this direction, heterologous booster study was completed, and the data is submitted. At a later point of time, a study on interchangeability in the primary schedule would also be considered on need basis.
Long-term safety	Long-term safety and effectiveness	Long-term safety profile of SKYCovione vaccine is currently limited and it is recognized that further follow-up for all vaccines is required. Additional activities will be needed to obtain such information. All the clinical study participants are being followed up for a period of 6-12 months after last dose. The generated long-term protection and safety data will be presented to the Indian NRA. Based on Subject Expert Committee, Indian NRA recommendation, BE may extend the monitoring for further 24-36 months. In addition, safety data from active monitoring of sentinel site will also be gathered on a regular basis to increase the safety database.
	Impact of the emergence of variants on vaccine efficacy/ effectiveness and safety	The applicant should provide to WHO any data on new emerging variants particularly from vaccine breakthrough cases as soon as available, irrespective of source.

3.4.1 Pharmacovigilance Plan

a. Routine activities

The applicant proposed the following routine activities:

- Spontaneous Reporting
- Literature search
- Monthly Summary Safety Reports (MSSRs)
- Periodic Safety Update Reports (PSUR)/ Periodic Benefit-Risk Evaluation Report (PBRER)
- Signal detection

The applicant mentioned that, if any executive and staff of SK bio (i.e., reporter in the company) obtain any product-related safety information from doctors, pharmacists, nurses, or consumers, he/she should report this to the division in charge of pharmacovigilance (PV) through the on-line Safety Information Reporting System (SIRS) within 24 hours of reporting (Day 0). A management number will be assigned automatically to the safety information entered in the SIRS according to rules of the company. If reporting via the SIRS is not available within 24 hours, information may be reported to the division in charge of PV by other methods such as telephone, e-mail, fax, or verbal communication.

SK Bio shall set up the receipt of safety reports from regulatory authority portal such as Eudravigilance or Medicinal and Healthcare products Regulatory Agency (MHRA) ICSR Portal after marketing authorization is granted from applicable regulatory authorities. The PV team shall access the online application once a day to download the reported relevant cases for processing.

However, optional activities should be further clarified whether these are part of the systematic collection of data, what methodology should be applied and the detailed explanation of signal detection. In addition, the applicant is requested to mention if these reports will be collected at global level, or if these activities will be implemented only in the Republic of Korea. The applicant should consider national and international Good Pharmacovigilance (GPV) guidelines for an adequate implementation of these activities in all WHO regions.

The applicant needs to explain how the safe data information will be collected and analysed, such as pregnancy reports, fatal cases, or potential interactions. In the case of pregnancy exposure, how will the pregnancy registry be implemented.

As part of the routine pharmacovigilance (PV) activities, the monitoring of adverse events (AEs) of interest needs to consider/include? facial paralysis, Guillain-Barre Syndrome, and neurological disorders, Transverse myelitis, Encephalitis, Acute disseminated encephalomyelitis (ADEM), Multiple sclerosis, Bell's palsy, Arthritis (rheumatoid, polymyalgia, reactive), Myocarditis/Pericarditis, Thyroiditis, Cerebrovascular events, Immune thrombocytopenia, Thromboembolic events and thrombosis with Thrombocytopenia Syndrome (TTS), anxiety, reactogenicity following vaccination among others, and all serious adverse events.

The applicant should submit the Monthly Safety Summary Report (MSSR) to WHO. The MSSR should include timely and continuous benefit risk evaluations. Topics covered by monthly summary safety reports will include:

- Interval and cumulative number of reports, stratified by report type (medically confirmed/not) and by seriousness (including fatal separately);
- Interval and cumulative number of reports, overall and by age groups and in special populations (e.g., pregnant women);
- Interval and cumulative number of reports per High-Level Term (HLT) and System Organ Class (SOC);
- Summary of the designated medical events;
- Exposure data based on distributed doses stratified by global regions;
- Changes to reference safety information and actions in the interval, and current CCDS;
- 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 HAs will be addressed in the MSSR;

- AESI reports –Summaries of reported cases of all AESI and RMP safety concerns: report numbers and relevant cases. If a disproportionality increased ratio is detected, a further evaluation of the concern will be presented as deemed applicable;
- Fatal reports – numbers and relevant cases (considering co-morbidities and frailty), further evaluation of the concern will be presented as deemed applicable;
- Data on medication errors will be included only if a pattern of errors leading to harm is identified and/or risk minimisation activities are considered warranted (e.g. changes to the PI; DHCP); otherwise, this data will be included with the (six-monthly) periodic safety update report (PSUR).
- Risk/benefit considerations.

The submission of MSSRs complements the submission of the 6 monthly periodic safety update reports (PSURs). The need and frequency of submission of these reports will be re-evaluated based on the available evidence from post-marketing after 6 months (6 monthly submissions). The Periodic Benefit Risk Evaluation Reports (PBRERs) of SKYCovione™ (GBP510) adjuvanted with AS03 should be submitted to WHO every 6 months for the first 2 years following the approval by MFDS and thereafter annually as a routine PV activity. The reports should be submitted to the MFDS within 1 month after the end of the each reporting period and submitted to WHO as well.

The applicant is requested to implement appropriate methods to ensure adequate traceability and needs to clarify how these traceability enhancements will be applied to shipments through the COVAX facility or other international deployments.

The applicant needs to commit to conduct additional pharmacovigilance interventions to collect AEs in low- and middle-income countries (LMICs). This is important to address the need for adequate pharmacovigilance systems in LMICs and the limited information from the clinical trials and post-authorization information that have been collected.

The applicant did not indicate how they will monitor and evaluate the impact of emerging SARS-CoV-2 variants (such as B.1.1.7, B.1.351 and P.1, and others that may appear in the future) on the effectiveness of SKYCovione™ and how they intend to discuss with WHO plans to make changes to the vaccine to address this issue.

3.4.2 Additional pharmacovigilance activities

Additional pharmacovigilance activities proposed by the applicant include ongoing studies and Post-marketing Surveillance – Database Study.

- *Ongoing studies*
    - *GBP510_002; A 3-Stage, Phase I/II, Placebo-controlled, Randomized, Observer-blinded, Dose-finding Study to Assess the Safety, Reactogenicity, and Immunogenicity of a SARS-CoV-2 Recombinant Protein Nanoparticle Vaccine (GBP510) adjuvanted with or without AS03 in Healthy Younger and Older Adults.* This study was initiated on 3rd Feb, 2021 (First patient enrolment) and completed enrolment on 28th July, 2021 at 14 sites across the South Korea. Primary CSR: 09Feb2022, Final CSR estimated date: April 2023.
    - *GBP510_003; A 2-Stage, Phase III, Randomized, Active-controlled, Observer-blind, Parallel-group, Multi-center Study to Assess the Immunogenicity and Safety of SK SARS-*

CoV-2 Recombinant Protein Nanoparticle Vaccine adjuvanted with AS03 (GBP510) in Adults Aged 18 Years and Older. This study was initiated on 30th August, 2021 (First patient enrolment) and completed enrolment on 14th January, 2022 at 39 sites in 6 countries (Korea, Vietnam, Thailand, Philippines, Ukraine and New Zealand). Primary CSR: 02Jun2022, Final CSR estimated date: May 2024.

- *Post-marketing Surveillance – Database Study Passive Surveillance Methods*
    - *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 protocol is not available yet. The draft study protocol was submitted, and the next version is planned to be submitted 3 months following receipt of first regulatory authorization. The final Report estimated submission date is 3rd quarter 2025. Therefore, it is not possible to assess what kind of observational study is planned, safety concern, design, population, or countries. It is not mentioned if these activities will be included in different WHO regions.
- *Effectiveness of SKYCovione COVID-19 Vaccine in South Korea.* The applicant has submitted a draft of the protocol. The primary endpoint is to estimate the vaccine effectiveness (VE) of a 2-dose primary series of SKYCovione COVID-19 vaccine to prevent confirmed COVID-19 (confirmation by PCR or other assays), severe COVID-19, and all-cause death by comparing individuals vaccinated with SKYCovione COVID-19 vaccine versus those not vaccinated with any COVID-19 vaccine in a real-world setting of South Korea. The applicant is not considering this study as an additional pharmacovigilance activity.

3.4.3 Risk minimization activities

The routine risk minimization activities are sufficient to manage the safety concerns of the vaccine. The applicant is encouraged to consider developing educational materials aimed at minimizing the risk of immunization errors, such as printed posters or guides, in addition to providing information with the SmPC in all WHO regions.

3.4.4 Conclusion

The risk benefit assessment is partially acceptable. The applicant is requested to include additional activities to monitor and collect information of AEs in low- and middle-income countries (LMICs) of certain regions. The company is also urged to submit as soon as possible the final protocols of the observational studies and include how this study will be implemented in the different WHO regions. The applicant is requested to update the routine pharmacovigilance activities including signal detection.

A global pregnancy registry needs to be considered to collect the information in this population.

1. The RMP should also include/address the following:
    - Safety specifications
        - Identified risk: *Anaphylaxis*
        - Potential risks: add *programmatic error*

  - Missing information: add *use in paediatric population <18 years of age, Use in immunocompromised patients, including HIV, Use in patients with autoimmune or inflammatory disorders,* and *impact of the emergence of variants on vaccine efficacy/effectiveness and safety.*

- Pharmacovigilance plan
  - The applicant is urged to conduct additional pharmacovigilance activities (non-interventional and interventional in other WHO regions, and it is requested to submit as soon as possible the protocols.
- Risk minimization activities
  - A minimum period of 15-minutes of observation for each vaccinee after vaccination given the risk of potentially life-threatening anaphylactic/ anaphylactoid reactions should be recommended in the product insert.

In addition, in light of the recent evidence of vaccine escape of some emerging SARS-Cov-2 variants, the applicant is requested to closely monitor and evaluate the impact of these emerging SARS-CoV-2 variants (such as B.1.1.7, B.1.351 and P.1, and others that may appear in the future) on the effectiveness of SKYCovione™. and to discuss with WHO in case of plans to make changes to the vaccine to address this issue.

4 Outcome of review

4.1 Quality

Outcome of WHO review on programmatic aspects and suitability of SKYCovione™ for LMICs highlighted the absence of VVM and preservative, the vaccine being only available in a multidose presentation. Nevertheless, the applicant provided assurance that temperature during shipping from manufacturer to country storage facilities was strictly and closely monitored. The applicant recommends the used of the vaccine as soon as it is mixed with ASO3 adjuvant. Although the storage conditions are those similar to vaccine used in national immunization programmes (2 – 8 °C), these characteristics should be considered in the deployment and used of the vaccine in LMIC settings.

4.2 Clinical

This clinical assessment raised a number of queries and comments from the reviewers on clinical submitted evidence and issues related to the RMP. These have either been considerably addressed by SK bio's list of questions or have been incorporated into the recommendations listed below and in the conclusion section of this document. The available data may not be generalizable to other populations in low and middle-income countries (LMIC) who have profiles that can impact on the efficacy of this vaccine (for example, ethnicity, concomitant infections and malnutrition). The PEG recommends that an EUL may

be granted by WHO to GBP510 (COVID-19 Vaccine), if SK Bioscience commits to meet the following conditions post-EUL:

1. The applicant should submit to WHO the final clinical study reports of the ongoing studies once they are completed.
2. Any relevant data coming from post EUL effectiveness studies should be shared with WHO, as this might change the benefit/risk profile of the vaccine.
3. The applicant should provide data for the use of GBP510 as booster after primary series.

The RMP should also include/address the following:

- Safety specifications:
    - Identified risk: *Anaphylaxis*
    - Potential risks: add *programmatic error*
    - Missing information: add *use in paediatric population <18 years of age, Use in immunocompromised patients, including HIV, Use in patients with autoimmune or inflammatory disorders,* and *impact of the emergence of variants on vaccine efficacy/effectiveness and safety.*
- Pharmacovigilance plan
    - The applicant is urged to conduct additional pharmacovigilance activities (non-interventional and interventional in other WHO regions, and it is requested to submit as soon as possible the protocols.
- Risk minimization activities
    - A minimum period of 15-minutes of observation for each vaccinee after vaccination given the risk of potentially life-threatening anaphylactic/ anaphylactoid reactions should be recommended in the product insert.

In addition, in light of the recent evidence of vaccine escape of some emerging SARS-Cov-2 variants, the applicant is requested to closely monitor and evaluate the impact of these emerging SARS-CoV-2 variants (such as B.1.1.7, B.1.351 and P.1, and others that may appear in the future) on the effectiveness of Ad26.COV2.S. and to discuss with WHO in case of plans to make changes to the vaccine to address this issue.

5 Technical considerations

The technical considerations included in this section are those proposed by the applicant. The TAG and the PEG's considerations are made in the "Comments" after each subsection.

5.1 Vaccine characteristics

Qualitative composition

Product composition (before mixing with ASO3 adjuvant)

1. Antigen vial (per 2.5 mL)

Active Ingredient:	SARS-CoV-2 Spike Protein Receptor Binding Domain (Recombinant) …250 µg
Stabilizer:	Arginine (*Ph. Eur*.)
	Sucrose (*Ph. Eur*.)
Excipients:	Sodium chloride (*Ph. Eur*.)
	Tromethamine (*Ph. Eur*.)
Solvent:	Water for injections (*Ph. Eur*.)

2. Adjuvant vial (per 2.5 mL)

Adjuvant system:	Squalene (In-house)
	DL-α-Tocopherol (*Ph. Eur*.)
	Polysorbate 80 (*Ph. Eur*.)
Excipients:	Sodium chloride (*Ph. Eur*.)
	Potassium chloride (*Ph. Eur*.)
	Disodium hydrogen phosphate (*Ph. Eur*.)
	Potassium dihydrogen phosphate (*Ph. Eur*.)
	Water for injections (*Ph. Eur*.)

Pharmaceutical Form:

Suspension and emulsion for emulsion for injection. The suspension (antigen) is clear or slightly opalescent liquid.

The emulsion (adjuvant) is whitish to yellowish homogeneous milky liquid.

The emulsion (antigen mixed with adjuvant) is a whitish to yellowish homogeneous milky liquid.

5.2 Special precautions for storage and handling proposed by the applicant

Shelf life

12 months when stored at 2 – 8 °C, or otherwise as marked on the vaccine vial.

Special precautions for storage

Keep refrigerated at 2°C to 8°C in a sealed container away from light. Do not freeze.

Special precautions for disposal and other handling

1) This drug is shielded from light and stored in the refrigerator (2~8℃) and should not be frozen. If frozen, the vaccine should be discarded.
2) Antigen and adjuvant (AS03) vials stored in refrigerator (2~8℃) should be kept at room temperature for about 15 minutes (to reach room temperature) before vaccine administration.
3) Storage condition after opening the vial: Mixed vaccine should be used within 6 hours after opening and mixing with adjuvant (AS03). If it has not been used within 6 hours, it should be discarded.
4) In the antigen/adjuvant mix vial, mark the mixed date and time.

General Precautions

1) Hypersensitivity and anaphylaxis: Events of anaphylaxis have been reported with COVID-19 vaccines. Appropriate medical treatment and intervention should always be readily available in a case where an anaphylactic reaction appears following vaccination. Careful and close observation for at least 15 minutes is required following vaccination. The second dose of the drug must not be injected to those who have experienced anaphylaxis to the first dose.
2) Anxiety-related reactions: Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions, may occur as a psychogenic response to a vaccination needle. Precautions are needed to be taken place to avoid injury caused by syncope.
3) Immunocompromised individuals: The efficacy, safety and immunogenicity of this vaccine has not been assessed for immunocompromised individuals, including those receiving immunosuppressant therapy. The vaccine may result in lower efficacy in those individuals.
4) Duration of protection: The duration of protection afforded by this vaccine is unknown.
5) Limitations of vaccine effectiveness: As with all other vaccines, this vaccine may not protect all vaccine recipients. Overall as well as strain specific efficacy was not evaluated as part of the clinical trial program.
6) Effects on ability to drive and use machines: This vaccine has no or negligible influence on the ability to drive and use the machinery, provided that, however, some of symptoms listed in Section 3 “Undesirable effects” may temporarily affect the ability to drive and use machines.

5.3 Indication, warnings and contraindications

Therapeutic indications
Active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals ≥ 18 years of age

Special warnings and precautions for use
Contraindications
1) Patients with hypersensitivity to active substances or to any of the excipients contained in this drug.

SKYCovione™ should be administered, with extra care, to those patients

1) Individuals suffering from an acute severe febrile illness (vaccination should be postponed for individuals with acute severe febrile illness or acute infection. However, the presence of a minor infection and/or low-grade fever should not delay vaccination.)
2) Patients who are receiving anticoagulants or have current thrombocytopenia or other blood clotting disorders (e.g., hemophilia) (extra caution is required since intramuscular may lead to bleeding or bruising)

5.4 Posology and method of administration

Posology

Individuals 18 years of age and older

This drug is administered in 2 doses of 0.5 mL each, with the second dose given four weeks after the first. No data available on the interchangeability of this drug with other COVID-19 vaccines. Individuals who have received the first dose (Dose 1) of this drug should receive the second dose (Dose 2) to complete the vaccination course.

Pediatric and Adolescent Populations

The safety and efficacy of this drug in children and adolescents aged below 18 years have not yet been established, no data is currently available.

Elderly Population

No dose adjustment is required in elderly individuals aged 65 years and above.

Method of Administration

This drug is administered intramuscularly, after mixing the antigen suspension of the vial with the adjuvant (AS03), preferably to the upper arm deltoid. Vaccines remaining in multiple vials should not be collected and used. This drug should under no circumstances be administered intravascularly, subcutaneously or intradermally. The vaccine should not be mixed in the same syringe with any other vaccines or medicinal products. For precautions related to administration, see Section 10. “Precautions for administration”.

Precautions for Administration

This drug is multidose vial and should be used by mixing one antigen vial with one accompanying adjuvant (AS03) and after mixing, the one vial contains 10 multiple doses (0.5 mL/dose). A single dose (0.5 mL) contains 25 micrograms of recombinant SARS-CoV-2 surface antigen protein nanoparticles. To ensure the sterility of the injection, the drug should be prepared by healthcare professional using aseptic techniques.

1) Both antigen and adjuvant vials should be stored at refrigerator (2 to 8℃) and should be kept at room temperature for about 15 minutes prior to mixing to reach room temperature.
2) The vaccine is mixed by withdrawing the entire contents of the vial containing the adjuvant by means of a 5 mL syringe and by adding it to the vial containing the antigen. The syringe with a 23-25G needle is recommended to be used.
3) Gently mix the antigen vial so that the antigen and the adjuvant are completely mixed.
4) After mixing, the volume of the vaccine is at least 5 mL. It should be a whitish to yellowish homogeneous milky liquid emulsion. The vial should be shaken prior to each administration and

inspected visually for any foreign particulate matter and /or abnormal physical appearance. In the event of either foreign particulate matter or abnormal physical appearance being observed visually (including rubber particles from the stopper), discard the vaccine.

5) Each vaccine dose of 0.5 mL is withdrawn from the antigen/adjuvant mix vial into a 1 mL syringe for injection and administered intramuscularly. The syringe with a needle 23-25G is recommended to be used.
6) At each injection, cleanse the vial stopper with a single use antiseptic swab and a new sterile needle and a sterile syringe are used to retrieve 0.5 mL (1 dose) from the antigen/adjuvant mix vial, and the drug taken by the syringe should be used immediately and not stored at refrigerator.
7) If the correct dose (0.5 mL) is not taken with the syringe, or discoloration or foreign matters are visually observed; the vaccine should not be administered.
8) The name and lot number of the product being administered should be clearly recorded to track the history of the vaccine.

5.5 Fertility, pregnancy and lactation

1) Pregnancy: This drug has only limited experience with the use in pregnant women.
   Animal studies do not indicate direct or indirect harmful effects for pregnancy, embryofoetal development, parturition or post-natal development. Administration of this drug should be considered only in a case where the potential benefits to the mother and fetus outweigh any potential risks.
2) Breast-feeding (lactation): It is unknown whether this drug is excreted in human milk.
3) Fertility: Animal studies do not indicate direct or indirect harmful effects for reproductive toxicity.

5.6 Interaction with other medicinal products and other forms of interaction

Study for drug interaction has not been conducted. Concomitant administration with other drugs or vaccines have not been studied.

5.7 Safety profile

The safety of this drug was assessed through the interim analysis of phase III clinical trial (Data cut-off date: 2022. 03. 18). 4,025 subjects who are 18 years old and older were administered this drug (N=3,029) or the active control vaccine (N=996) at least 1 dose. The median age of subjects is 37 (range: 18 to 88 years) and 5.3% (N=213) of elderly over the age of 65 were included.

As the result of safety evaluation for 4 weeks after primary vaccination, the most reported adverse events were injection site pain (55.7%), fatigue (31.1%), myalgia (30.5%), and headache (29.9%) and most of these adverse events were mild to moderate in severity and resolved within a few days after vaccination. Overall, the frequency of adverse events was higher in the younger adult group (18 to 64 years) than the elderly group (over 65) and the frequency of adverse events after 1 dose was higher than after 2 doses. Also, it was reported more in Korean and Caucasian than Southeast Asian.

Adverse events observed during clinical trials are summarized below according to the following frequency categories: Very Common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 1/1,000 to < 1/100), Rare

(≥ 1/10,000 to < 1/1,000), Very Rare (< 1/10,000), and Not Known (cannot be estimated from the currently available data).

System Organ Class	Very Common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,000)
Blood and Lymphatic System disorders				Lymphadenopathy
Nervous System Disorders	Headache		Dizziness, Paraesthesia	hypoesthesia
Gastrointestinal Disorders		Nausea/Vomiting, Diarrhea		Abdominal pain, Dyspepsia
Musculoskeletal and Connective Tissue Disorders	Arthralgia, Myalgia		Pain in extremity	Back pain, Groin pain
General Disorders and Administration Site Conditions	Injection site pain, Fever[1)], Fatigue, Chills[1)]	Injection site redness, Injection site swelling	Injection sitepruritus, Injection site warmth, Pain, Chest pain	Asthenia
Skin and Subcutaneous Tissue Disorders			Rash	Pruritus, Hyperhidrosis
Respiratory, thoracic and mediastinal disorders			Oropharyngeal pain, Cough	
Cardiac disorders			Palpitations	
Metabolism and nutrition disorders				Decreased appetite
Infections and infestations				Upper respiratory tract infection
Neoplasms benign, malignant and unspecified				Melanocytic naevus

[1)] Fever and chills were observed more frequently after 2 doses than 1 dose.

<Additional safety information>

Rapidly progressive glomerulonephritis (N=1) was reported as a serious adverse drug reaction after administration of this drug.

5.8 Overdose

No case of overdose has been reported yet. In the event of overdose, individual monitoring of vital functions and proper intervention depending on the observed symptoms are required.

Pharmacokinetic properties

Not applicable.

Pharmaceutical Particulars

Incompatibilities

This medicinal product must not be mixed with other medicinal products or diluted.

6 Monitoring of performance of the vaccine in the field

6.1 Vaccine efficacy/effectiveness and safety Monitoring

Information for Healthcare Professionals

1) Pharmacological Properties

This drug is nanoparticle formulation targeting the Receptor Binding Domain(RBD) of SARS-CoV-2 Spike (S) protein originated from the D614G strain. When administered, an adjuvant (AS03) composed of squalene, DL-α tocopherol and others is mixed and administered. This drug may give protection against COVID-19 by inducing humoral and cellular immune responses to RBD proteins, including neutralizing antibodies.

2) Clinical Trials Information

The submitted clinical trial data is the interim results of a multi-center, parallel, observer blind, active-controlled, randomized, on-going phase III clinical trial (GBP510_003) in adults aged 18 years and older and this has been conducting in the Republic of Korea, the Philippines, Thailand, Vietnam, Ukraine, and New Zealand. In this clinical trial, the immunogenicity and safety of this drug were assessed by comparing it with the active control group (Vaxzevria administered group), and the protection effect was not assessed.

In the immunogenicity analysis set, subjects without a history of COVID-19 infection and vaccine administration were randomly assigned to the test group and the control group at a ratio of 2:1 and administered twice with the second dose given 28 days after the first. The demographic and baseline characteristics were similar in two groups.

The median age was 41 years (range: 18 to 84 years) including 6.1% (119 people) of 65 years of age or older, 25.4% (497 people) of Koreans, 65.9% (1,288 people) of Southeast Asians, and 8.7% (171) of Caucasians.

The primary immunogenicity analysis group included 1,318 subjects (877 in test group and 441 in control group) who completed second doses, had no significant protocol violation, and had no evidence of SARS-CoV-2 infection until the immunogenicity assessment (2 weeks after second doses).

As a result of assessing neutralizing antibody titer for D614G strains of SARS-CoV-2 through the FRNT (Focus Reduction Neutralization Test) method at 2 weeks after second doses, the geometric mean titer (GMT) ratio of this vaccine compared to the control vaccine (Vaxzevria) is 2.93 (the lower limit of the two-sided 95% confidence interval of 2.63), satisfied the hypothesis of superiority (the lower limit of the 95% confidence interval > 1) and the difference of seroconversion rate* between the two groups is 10.76% (the lower limit of the two-sided 95% confidence interval of 7.68%), satisfied the hypothesis of non-inferiority (the lower limit of the 95% confidence interval > -5%).

* Seroconversion rate: Percentage of people whose neutralizing antibody titer for D614G strains increased by more than 4 times after vaccination compared to baseline (prior to vaccination

Table 2. Results of SARS-CoV-2 Neutralizing Antibodies Analysis at Two Weeks After the Second Doses

Contents		Test Group (SKYCovione Multi Injection) (N=877)	Control Group (Vaxzevria Injection) (N=441)
Neutralizing Antibodies*	GMT (95% Confidence Interval of GMT	272.12 (240.40, 308.02)	92.75 (80.79, 106.48)
	GMT Rate (95% CI)	2.93 (2.63, 3.27)	
Seroconversion Rate	Seroconversion Rate % (95% CI)	98.06 (96.91, 98.87)	87.30 (83.83, 90.26)
	Difference in Seroconversion Rate (95% CI)	10.76 (7.68, 14.32)	

* Neutralizig antibody titer was calculated by correcting the antibody titer before administration, and age groups.

3) Non-clinical Information

(1) General Toxicity

No special hazard was observed based on studies of repeat-dose toxicity.

(2) Genotoxicity and Carcinogenicity

Genotoxicity nor carcinogenicity studies were conducted.

(3) Reproductive and Developmental Toxicity

Reproductive and developmental toxicity studies were conducted with female rats administered four intramuscular doses (caesarean sectioning subgroup:

twice prior to mating, twice during gestation) or five intramuscular doses (natural birth subgroup: twice prior to mating, twice during gestation, one time during lactation) of 12 µg recombinant SARS-CoV-2 surface antigen protein nanoparticles with AS03 adjuvant.

For the caesarean sectioning subgroup, no vaccine-related effects were observed in female fertility, maternal functions, and development of embryo-foetal through 21 days of gestation. In the natural birth subgroup, no vaccine-related effects were observed in female fertility, maternal functions, survival, growth, and development of offspring through post-natal 21 days.

6.2 Programmatic aspects

The vaccine does not bear a Vaccine Vial Monitor (VVM) nor contain preservative. It should be used right after mixing.

7 Regulatory oversight

SKYCovione™ adjuvanted with AS03 was licensed by MFDS on June 29, 2022. The same product in terms of formulation, volume per dose, number of doses per container, route of administration and type of

container closure system, received a marketing authorization by the Medicines and Healthcare products Regulatory Agency (MHRA) of the United Kingdom (published 26 May 2023).

8 Benefit/Risk Assessment

According to the WHO Coronavirus (COVID-19) Dashboard (https://covid19.who.int/), the COVID-19 pandemic has caused, as of 19 March 2023, over 760 million confirmed cases and over 6.8 million deaths have been reported globally. COVID-19, caused by a novel coronavirus, SARS-CoV-2, transmitted easily worldwide to a naïve population, has become a major cause of morbidity and mortality while vaccines were not available and in the absence of proved specific treatment. Where COVID-19 vaccines have been administered in large scale and a large proportion of their population have been vaccinated the occurrence of hospitalizations and deaths by COVID-19 have decreased substantially, particularly in vaccinated individuals. Notwithstanding the fact that new SARS-CoV-2 variants that have the ability of evading immunity have replaced previously dominant ones – since December 2021 sublineages of the Omicron variant of concern (VOC) have been the most prevalent worldwide – approved COVID-19 vaccines have decreased substantially severe cases and deaths by COVID-19 in vaccinated populations. The need for a (homologous or heterologous) booster dose has been identified. The development and availability of effective and safe new vaccines may decrease the spread of COVID-19 and its morbidity and mortality.

As for any other vaccines, adverse events following immunization can be expected with COVID-19 vaccines. This can occur immediately following injection, caused by the reactogenicity of the vaccine materials or through allergy to some components of the vaccine. In addition, long-term ill-effects may be detected months or years following vaccination. Of concern particularly for inactivated vaccines, by analogy with past experience with vaccines for other diseases and with other coronaviruses candidate vaccines, is VAED or VAERD. Limited data do not indicate a propensity for SKYCovione™ to induce VAERD in animal models. A theoretical concern that is common to other COVID-19 vaccines is the safety of SKYCovione™ in pregnant and lactating women, who are also a target population to be immunized against COVID-19.

SKYCovione™ clinical trials have demonstrated that this vaccine induces a strong immunological response even against VOCs. The Neutralizing antibody response has fulfilled the criteria for immunobridging. CMI responses after vaccination suggest an increased Th1 response and a Th2 response kept at a low level. There is still limited evidence to support that the antibody response lasts for at least 6 months. SKYCovione™ available safety data is reassuring, but the size of the safety database of participants from clinical trials (over 3100 individuals) is limited compared to what was available at this point of the clinical development of other COVID-19 vaccines that had to demonstrate efficacy in randomized clinical trials, which required a larger sample size.

As is the case for all vaccines approved by immunobridging, vaccine effectiveness should be demonstrated in the post-authorization period, as no efficacy data is available. SK Bio has proposed the conduct of post-authorization studies that may provide that information. Such evidence should also come from low- and middle-income countries (LMICs). It is important that these studies, and/or others that may be conducted, provide evidence of SKYCovione™ induced protection against severe and fatal cases of COVID-19 in all age groups, immunocompromised individuals, people living with HIV, pregnant and

lactating women. Other studies should be conducted to assess the co-administration with other vaccines and sequential use/interchangeability with other COVID-19 vaccines, for which no current data exists.

9 Conclusion

Considering the public health need to halt COVID-19 morbidity and mortality and to continue immunizing the world's population to the largest extent possible, the introduction of new vaccines that would protect the population from disease is needed.

Based on the available evidence assessed, the TAG finds that sufficient data is available on COVID-19 vaccine SKYCovione™ for an EUL recommendation, subject to post-listing commitments as indicated in the below sections.

Should new evidence become available that change the benefit-risk assessment (e.g. as a result of the new variants) the EUL recommendation could be reconsidered.

9.1 Quality (CMC) perspective

9.1.1 Level of regulatory compliance

The PEG concludes that the Modules 1, 2 and 3 of the WHO EUL submission for SKYCovione™ contain the essential information to support the EUL application. These modules have been updated as per the responses to the PEG list of questions. Manufacturing sites have been inspected and were found GMP-compliant. The process, materials, containers, standards, and control tests have been described in detail. The product has been characterized and stability studies have been initiated. In general, the overall level of regulatory compliance is deemed acceptable. The applicant has adequately addressed the issues raised in the different round of questions.

9.1.2 Overall conclusion

The DS and DP manufacturing processes and process controls are described in detail. The manufacturing site for production of SKYCovione™ is located at SK Bio vaccine manufacturing plant, at 150, Sanupdanji-gil, Poongsan-eup, Andong-si, Geongsang-bukdo, Republic of Korea. This site has valid GMP certificate.

Raw materials are sufficiently described and controlled. The cell bank system and virus bank system were extensively tested and qualified. Critical process parameters were identified, drug substance and drug product processes are validated. Batch and comparability analyses were performed and submitted which indicated that the product from commercial scale is comparable to clinical materials.

The drug substance and drug product specifications proposed by the applicant are deemed acceptable, and the analytical methods for release and stability testing were described. Analytical methods are validated. Reference standards are described.

Container closure systems of drug substance and drug product were properly qualified (including extractables / leachable testing).

The currently proposed shelf lives for the DS (6 months, 2 - 8°C) and DP (12 months, 2 - 8°C) are supported by real time/real conditions stability studies of clinical trial batches and preliminary data from PPQ batches. The proposed shelf lives are deemed acceptable in the context of this EUL application.

In conclusion, based on the review of the quality data provided by the applicant, PEG has a positive opinion for the listing of SKYCovione™ under the EUL procedure.

Because of the available limited data at accelerated and stressed storage conditions, the EUL holder is asked to provide complementary stability data, as this becomes available. Any extension of the shelf-life for the drug substance and drug product should be justified by the corresponding real time data and submitted to WHO through a variation procedure as indicated in the Post EUL submissions procedure[22].

WHO will follow up on the commitments of the EUL applicant to continue the monitoring of the manufacturing process and make the corresponding adjustments, as soon as more date becomes available. The same apply to the controls of the drugs substance and drug product, for which more lots are necessary to make necessary evaluation of the adequacy of some of the quality specifications.

As for any variation altering the conditions for which this EUL is granted, vaccine batches will not be procured by UN procuring agencies or by COVAX if variations are not previously assessed and approved by both, the National Regulatory Authority of the vaccine producing country (MFDS) and by WHO.

In the event of any out of specifications (OOS) and quality related complaints, a thoroughly investigation should be triggered immediately, and any required action should be communicated to the WHO.

9.2 Clinical perspective

From the clinical point of review the PEG recommended that an EUL may be granted by WHO to COVID-19 Vaccine SKYCovione provided that SK Bioscience commits to provide the following requested information post-EUL as soon as such information becomes available:

1. The applicant should submit to WHO the final copies of clinical study report of GBP510_002 (12 months safety and immunogenicity of primary series by 30 June 2023; 12 months immunogenicity by 30 September 2023) and GBP510_003 (6 months immunogenicity by 30 June 2023, 12 months immunogenicity by 30 September 2023, 6 months immunogenicity of booster dose December 2023: 12 months immunogenicity by 30 September 2024).
2. Once available any relevant data coming from post EUL effectiveness studies (at most 36 months (about 3 years) from the date of EUL), should be shared with WHO, as this might change the benefit/risk profile of the vaccine in specific populations.
3. The applicant should investigate and provide to WHO, on a regular basis or whenever relevant information is available, updated data on the efficacy of the vaccine against disease caused by emerging SARS-CoV-2 variants of concern. This is important information given that decreasing

[22] https://extranet.who.int/pqweb/key-resources/documents/post-eul-submissions-procedure-vaccines

effectiveness may change the benefit/risk assessment in countries where these variants are predominant.

4. The applicant is urged to encourage participants, especially those not prioritized for vaccine access, to remain in the ongoing randomized controlled clinical trials as originally randomized for as long as possible, in order to accumulate at least 6 months of safety follow-up data after Dose 2 of the vaccine.
5. The RMP should also include/address the following:
    - Safety specifications:
        - Identified risk: *Anaphylaxis*
        - Potential risks: add *programmatic error*
        - Missing information: add *use in paediatric population <18 years of age, use in immunocompromised patients, including HIV, Use in patients with autoimmune or inflammatory disorders,* and *impact of the emergence of variants on vaccine efficacy/effectiveness and safety.*
    - Pharmacovigilance plan
    - *The applicant is urged to conduct additional pharmacovigilance activities (non-interventional and interventional in other WHO regions, and it is requested to submit as soon as possible the protocols.*
    - Risk minimization activities
    - *A minimum period of 15-minutes of observation for each vaccinee after vaccination given the risk of potentially life-threatening anaphylactic/ anaphylactoid reactions should be recommended in the product insert.*

In addition, in light of the recent evidence of vaccine escape of some emerging SARS-Cov-2 variants, the applicant is requested to closely monitor and evaluate the impact of these emerging SARS-CoV-2 variants on the effectiveness of SKYCovione, and to discuss with WHO in case of plans to make changes to the vaccine to address this issue. In addition, data on the use of the vaccine as a booster vaccine will be very important.